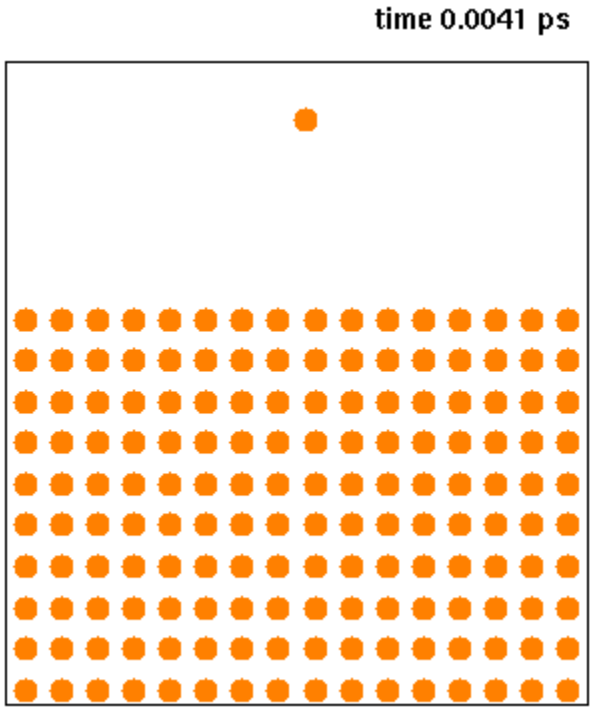
Summary of Elastic Network Model
Mayukhmali Das

Elastic Network models have been used to predict the global dynamics of a variety of proteins and protein complexes, ranging in size from single enzymes to macromolecular machines

1. ENM provide insight about protein behaviours
2. ENM allow the global motions of a molecule to be quickly calculated making them an ideal complement to conventional molecular dynamics (MD) simulations

   Molecular dynamics (**MD**) is a computer simulation method for analyzing the physical movements of atoms and molecules. The atoms and molecules are allowed to interact for a fixed period of time, giving a view of the dynamic "evolution" of the system. In the most common version, the trajectories of atoms and molecules are determined by numerically solving Newton's equations of motion for a system of interacting particles, where forces between the particles and their potential energies are often calculated using interatomic potentials or molecular mechanics force fields. The method is applied mostly in chemical physics, materials science, and biophysics.



3. At its core, the ENM provides a simplified representation of the potential energy function of a system, in this case a macromolecule or macromolecular assembly, near equilibrium. The nodes of the network are the building blocks, such as atoms, nucleotides or amino acids, from which the system is composed . Each node is typically represented as a point particle in three dimensions (3D), and the edges of the network, or the springs joining the nodes, represent harmonic restraints on displacements from the equilibrium structure

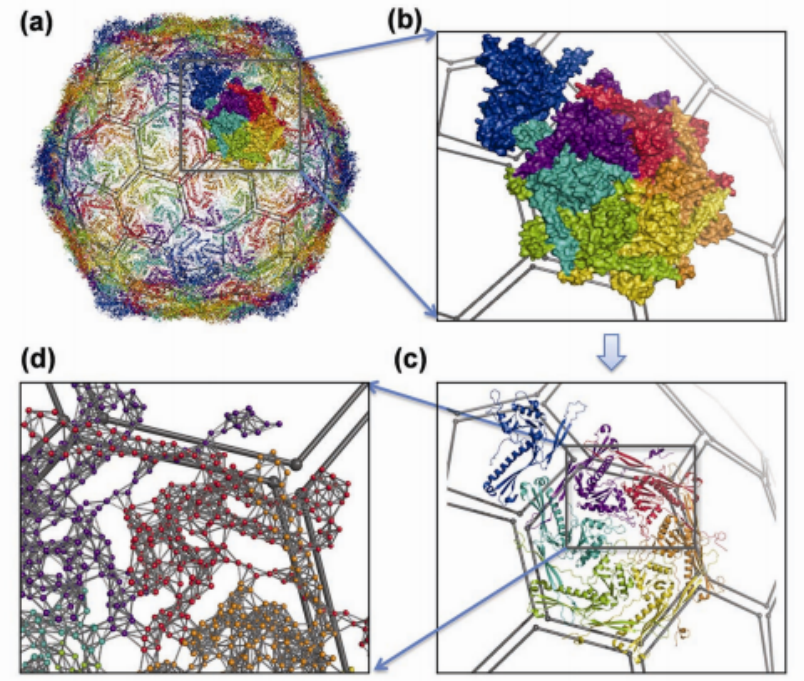


Fig. 7.1. ***From protein assemblies to network models.*** (a) External view of the intact viral capsid HK97 colored by chain, generated using the PDB file 2FT1 deposited by Johnson and coworkers (Gan *et al.* 2006). The capsid consists of 420 identical proteins arranged into 12 pentamers and 60 hexamers. (b) One asymmetric unit from panel (a) is enlarged. Each chain is in a distinctive color, indicating a possible scheme for rigid building blocks. (c) One asymmetric unit shown as secondary structures, in the same viewpoint and color scheme of panel (b). (d) A cartoon of the ENM in which the nodes are C^{α} atoms (spherical dots) and the edges represent the springs (or elastic couplings) connecting pairs of nodes located within a distance of r_c.

4.

What is Harmonic Well ? :

In classical mechanics, a **harmonic oscillator** is a system that, when displaced from its equilibrium position, experiences a restoring force *F* proportional to the displacement *x*:

$$\vec{F} = -k\vec{x},$$

where *k* is a positive constant.

If *F* is the only force acting on the system, the system is called a **simple harmonic oscillator**, and it undergoes simple harmonic motion: sinusoidal oscillations about the equilibrium point, with a constant amplitude and a constant frequency (which does not depend on the amplitude).

Quantum mechanics :

A diatomic molecule vibrates somewhat like two masses on a spring with a potential energy that depends upon the square of the displacement from equilibrium. But the energy levels are quantized at equally spaced values. The energy levels of the quantum harmonic oscillator are

$$E_n = (n + \tfrac{1}{2})\hbar\omega \qquad n = 0,1,2,3 \ldots$$

$\omega = 2\pi \cdot$frequency

$\hbar =$ Planck's constant $/2\pi$

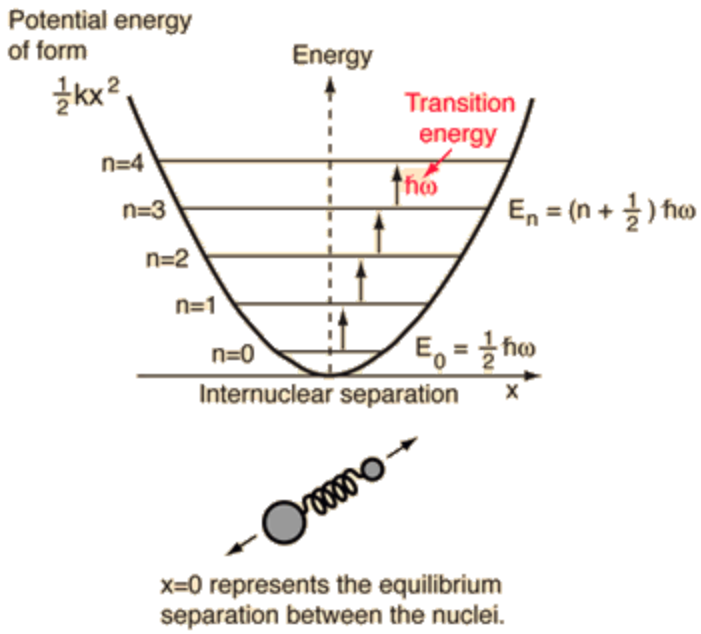
and for a diatomic molecule the natural frequency is of the form

$$\omega = \sqrt{\frac{k}{m_r}}$$

k = bond force constant

m_r = reduced mass

ENM provides an intuitive and quantitative description of behavior near equilibrium: The starting conformation resides at the bottom of a harmonic well, and any deviations from equilibrium will increase the energy and result in a linear net force directed toward restoring the system to its lowest energy state.



1. Harmonic Potential concept is being used for physics for a long time for for calculating elastic properties of bulk polymers and classical lattice vibrations

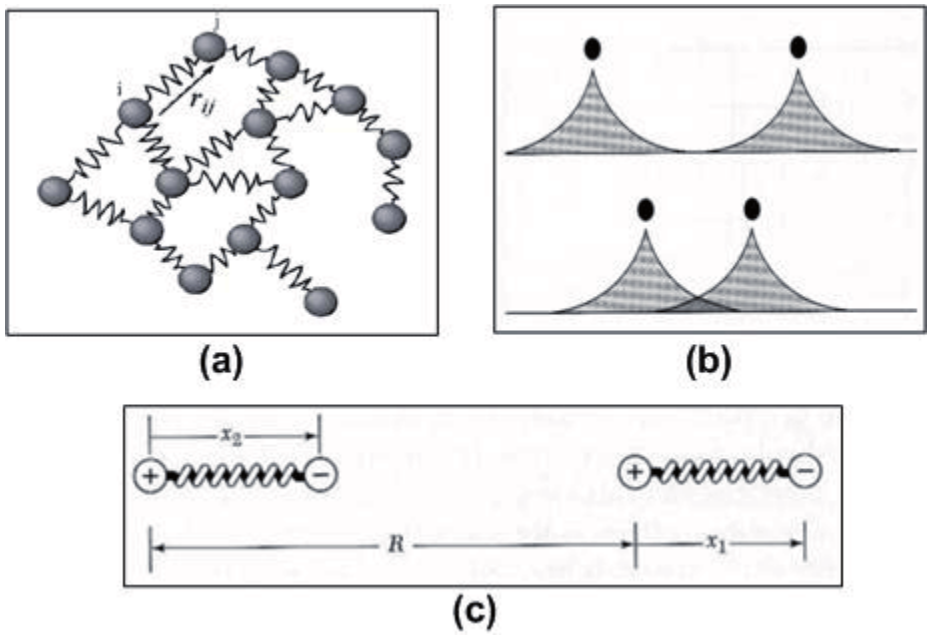
2. Now , on a later stage it was discovered that harmonic approximations can be applied even to proteins which are less flexible ; which saw the use of ENM for theoretical investigations of protein dynamics

3. There is a correlation between protein structure and its function and so ENMs provide an easily employable conduit between structure and dynamics of protein

4. Thus ENM is very much computationally cost effective

How is ENM created ?

Construction of the ENM is a matter of straightforwardly defining and linking nodes provided that information on structure, or simply on inter-residue contact topology, is available



(a) Elastic Network model with schematic representation. Every node is connected to its spatial neighbors by uniform springs. being a distance vector between nodes i and j
(b) Solid circles being nuclei, electronic charge distributions overlap as atoms approach representing repulsive interaction
(c) Representation of the atoms as oscillators in Van der Waals-London interaction modeling

How to get dynamic and static data from ENM ?

The standard technique for determining dynamics or statistical distributions from an ENM is to conduct a mode decomposition using **spectral graph theory** and methods (e.g., Gaussian Network Model (GNM) inspired by polymer network theory or a normal mode analysis (NMA) with uniform harmonic potentials, both of which provide analytical solutions to the equations of motion, bypassing the need to sample conformation space

Some basic definitions :

Spectral Graph Theory :

In mathematics, **spectral graph theory** is the study of the properties of a graph in relationship to the characteristic polynomial, eigenvalues, and eigenvectors of matrices associated with the graph, such as its adjacency matrix or Laplacian matrix.

The adjacency matrix of a simple graph is a real symmetric matrix and is therefore orthogonally diagonalizable; its eigenvalues are real algebraic integers.

While the adjacency matrix depends on the vertex labeling, its spectrum is a graph invariant, although not a complete one.

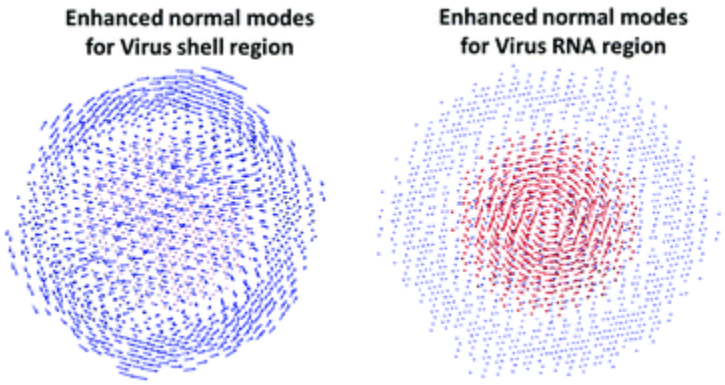
Spectral graph theory is also concerned with graph parameters that are defined via multiplicities of eigenvalues of matrices associated with the graph, such as the Colin de Verdière number.

Gaussian Network Model :

The **Gaussian network model (GNM)** is a representation of a biological macromolecule as an elastic mass-and-spring network to study, understand, and characterize the mechanical aspects of its long-time large-scale dynamics. The model has a wide range of applications from small proteins such as enzymes composed of a single domain, to large macromolecular assemblies such as a ribosome or a viral capsid. Protein domain dynamics plays key roles in a multitude of molecular recognition and cell signalling processes. Protein domains, connected by intrinsically disordered flexible linker domains, induce long-range allostery via protein domain dynamics. The resultant dynamic modes cannot be generally predicted from static structures of either the entire protein or individual domains.

Normal Mode Analysis :

Normal mode analysis (NMA) is one of the major simulation techniques used to probe large-scale motions in biomolecules. Typical application is for the prediction of functional motions in proteins.



NMA and ENM comparison :

In NMA calculations an initial energy minimization is required which distorts the input conformation, or else they risk producing energetically unstable solutions.

In comparison to NMA , ENM can take any conformation as input and is much more flexible

Problems with ENM :

1. Cannot provide reliable descriptions of local motions

2. The harmonic approximation requires a potential minimum, limiting the utility of ENMs for modeling non-equilibrium dynamics

3. Motions not in the neighborhood of the global energy minimum can be accurately predicted by the ENMs

Explaining the maths of ENM :

To be Done

Applications of ENM :

1. These models have been used to predict the global dynamics of a variety of proteins and protein complexes, ranging in size from single enzymes to macromolecular machines , ribosomes and viral capsids

2. They have provided insights into a wide range of protein behaviors, such as mechanisms of allosteric regulation , protein-protein binding , anisotropic response to uniaxial tension and unfolding , colocalization of catalytic sites and key mechanical sites , interactions at the binding sites , and energetics