

# A survey of structure and dynamics in HIV-1 Reverse Transcriptase



James M. Seckler<sup>1</sup>, Hongyu Miao<sup>1</sup>, Alan Grossfield<sup>2</sup>  
University of Rochester Medical Center, Rochester, NY, USA



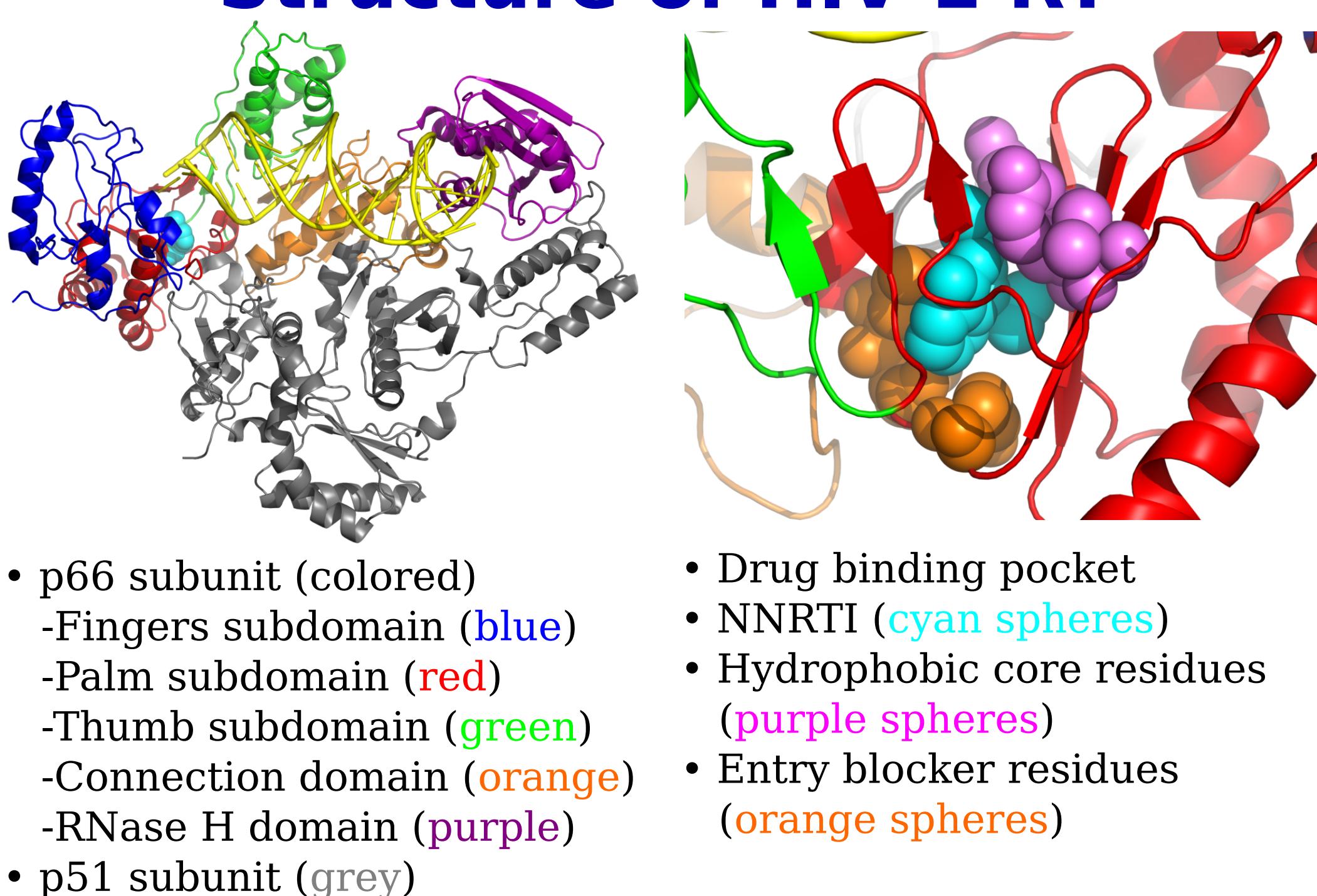
<sup>1</sup>Department of Biostatistics and Computational Biology

<sup>2</sup>Department of Biophysics and Biochemistry

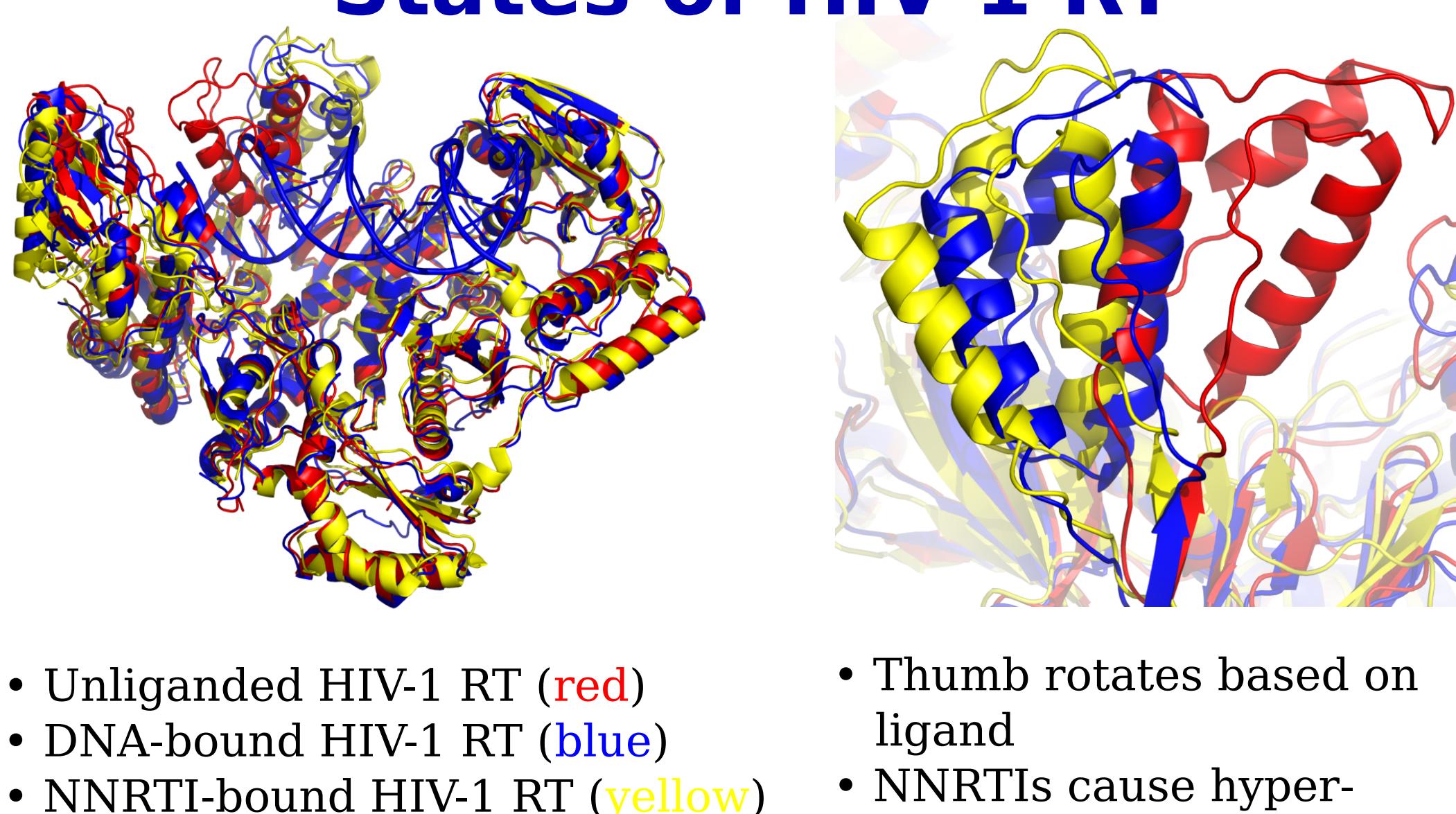
## Abstract

HIV-1 reverse transcriptase (RT) is a critical drug target for HIV treatment, and understanding the exact mechanisms of its function and inhibition would significantly accelerate the development of new anti-HIV drugs. Structural information on reverse transcriptase alone has proven to be insufficient to explain the mechanism of inhibition and drug resistance of non-nucleoside reverse transcriptase inhibitors. Elastic network modeling provides a technique to rapidly probe and compare protein dynamics. Combining elastic network modeling with hierarchical clusters of both structural and dynamic data reveals a wealth of novel information. Here we present an extensive survey of the dynamics of reverse transcriptase bound to a variety of ligands with a number of mutations, revealing a novel mechanism for drug resistance to non-nucleoside reverse transcriptase inhibitors, where hydrophobic core mutations subtly shift the position of the thumb subdomain, restoring active-state motion to multiple functionally significant regions of HIV-1 RT. This model arises out of a combination of structural and dynamic information, rather than exclusively from one or the other.

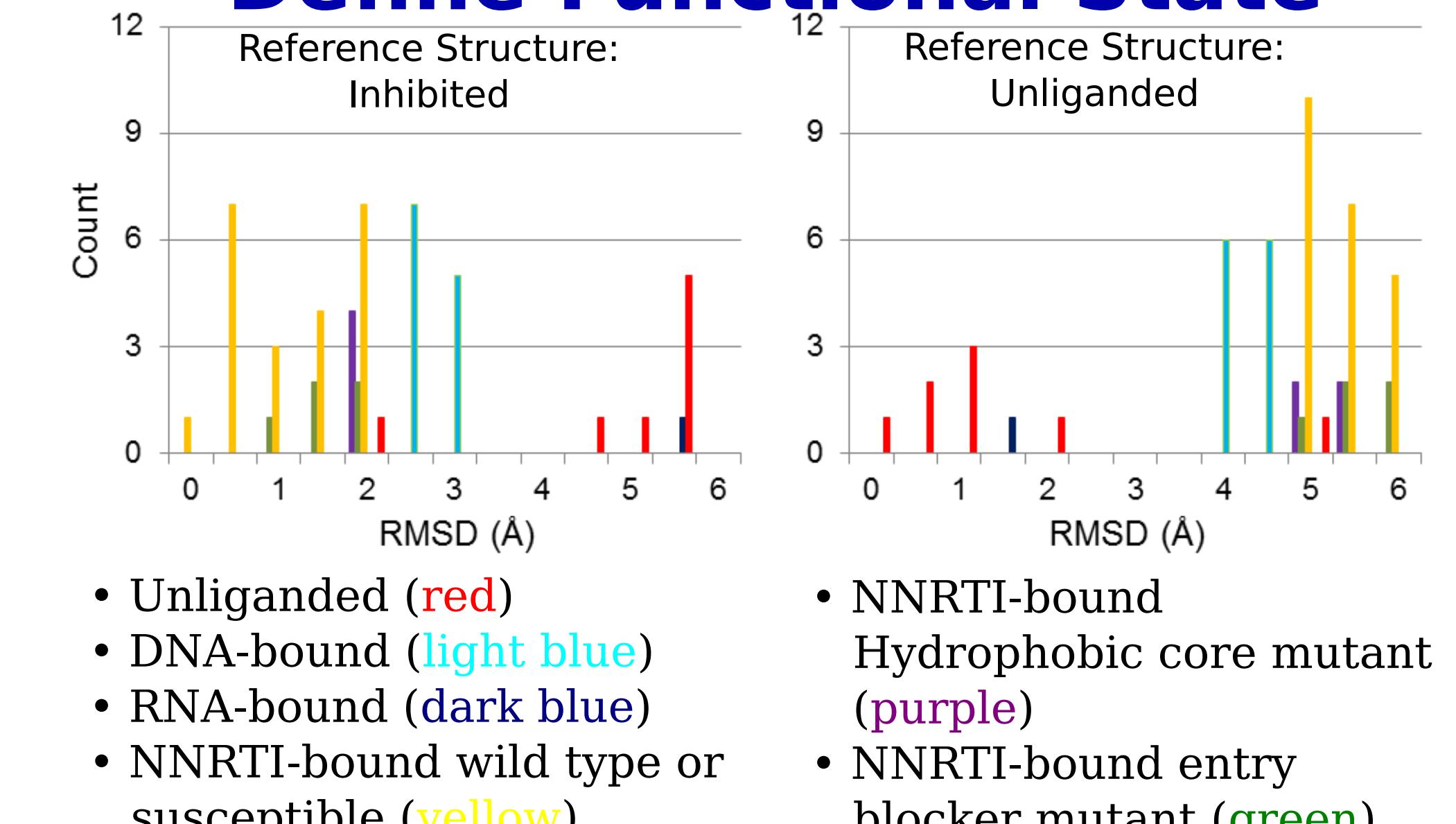
## Structure of HIV-1 RT



## States of HIV-1 RT



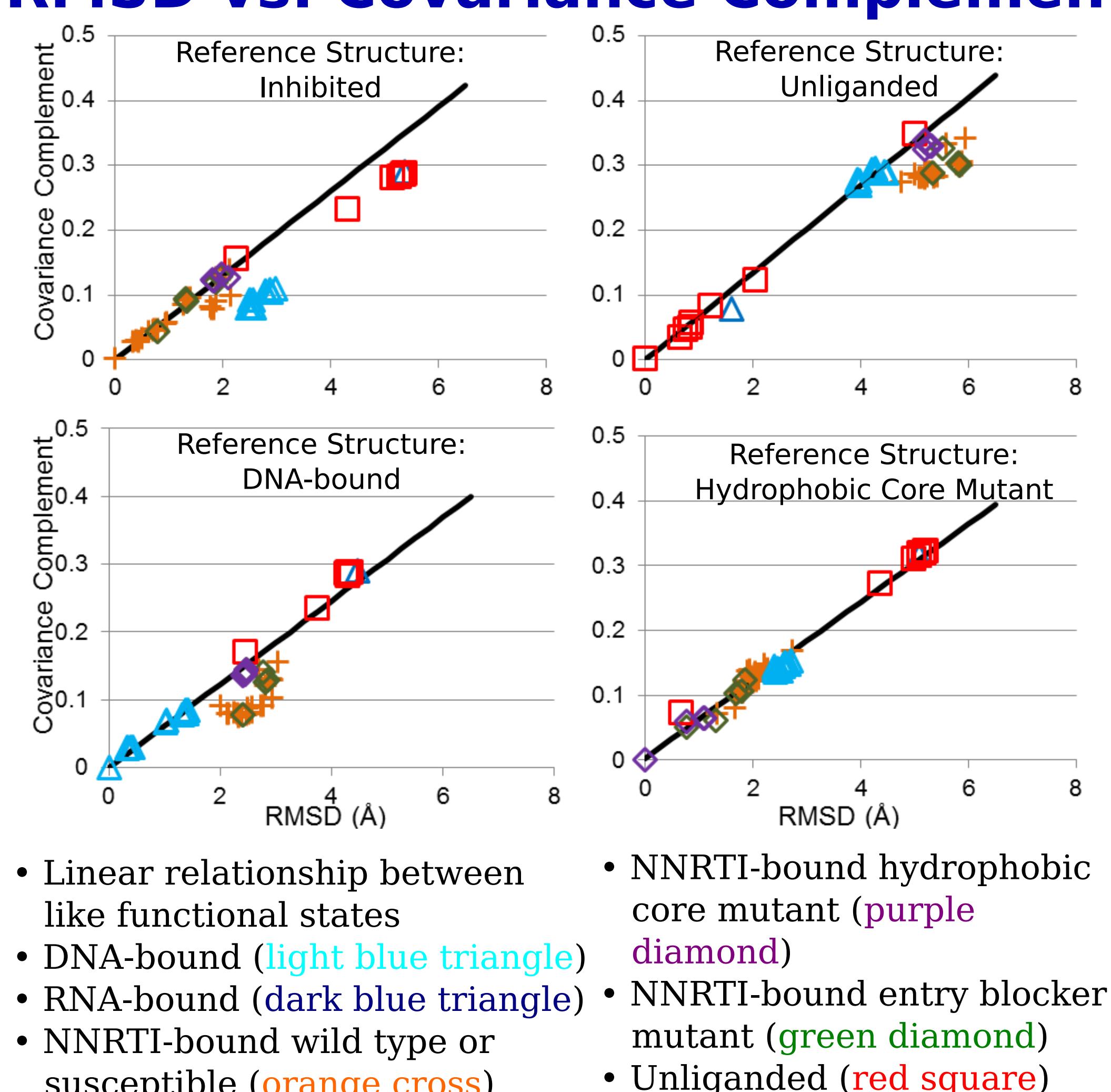
## Structural Comparison Cannot Define Functional State



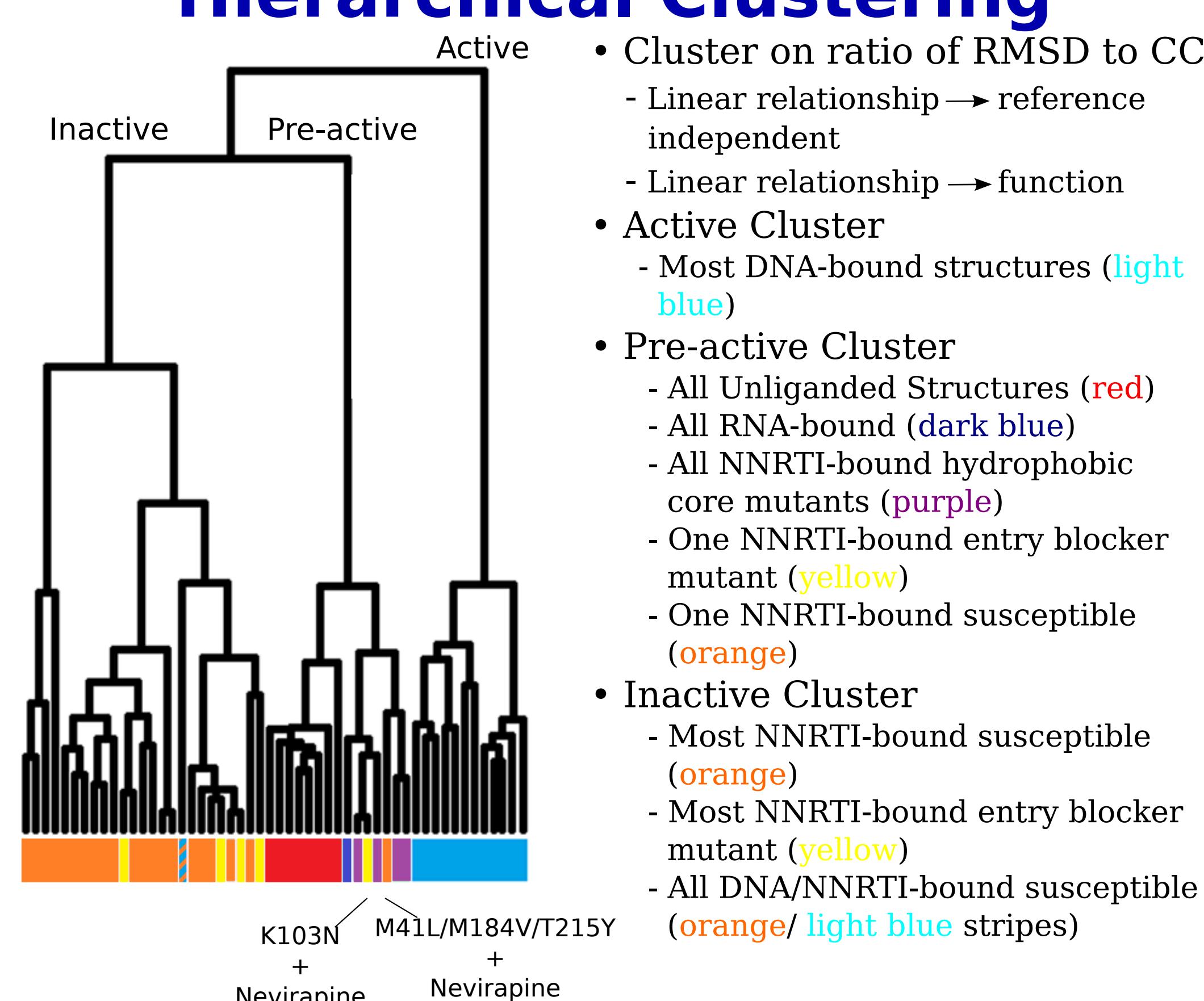
## Elastic Network Models

- All-atom Molecular Dynamics (MD) too slow
- Coarse-grained model, Cα resolution, fast
- "Beads on springs"
- Single harmonic potential:  $CC_{A,B} = \left[ \frac{\sum_i^N (\lambda_i^A + \lambda_i^B) - \sum_i^N \sum_j^N \sqrt{\lambda_i^A \lambda_j^B (\vec{v}_i^A \cdot \vec{v}_j^B)^2}}{\sum_i^N (\lambda_i^A + \lambda_i^B)} \right]^{1/2}$
- $U_{ij} = k(r_{ij}) (|r_{ij}| - |r_{ij}^0|)^2$
- $k(r_{ij}) = \begin{cases} 1 & : r_{ij} < r_c \\ 0 & : r_{ij} \geq r_c \end{cases}$
- $k$  is a uniform spring constant
- $r_{ij}^0$  minimum energy - starting structure
- Diagonalize Hessian Matrix
- Yields eigenpairs
- Eigenvalues describe frequency
- Low frequencies → collective dynamics
- Eigenvectors describe direction

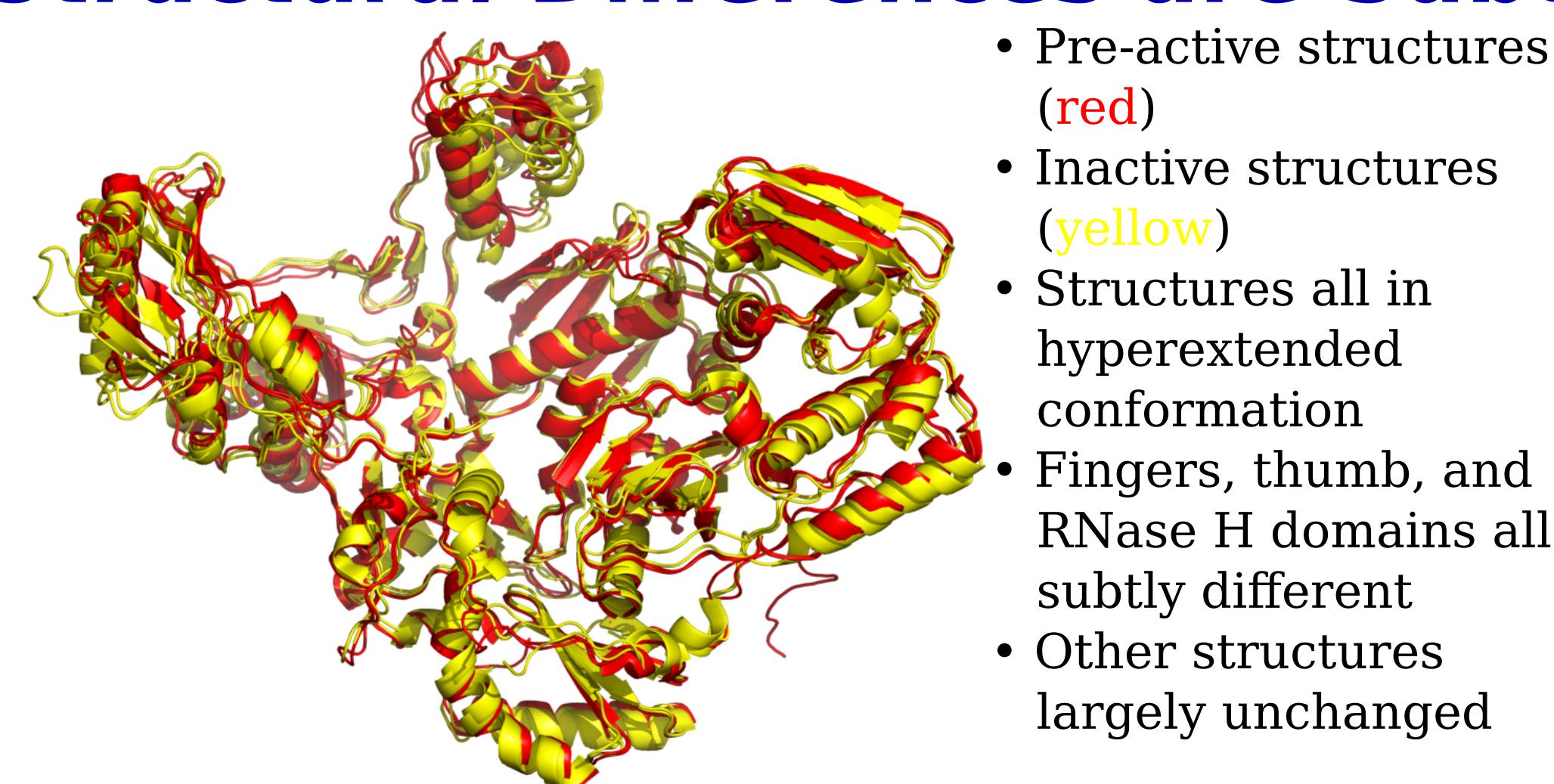
## RMSD vs. Covariance Complement



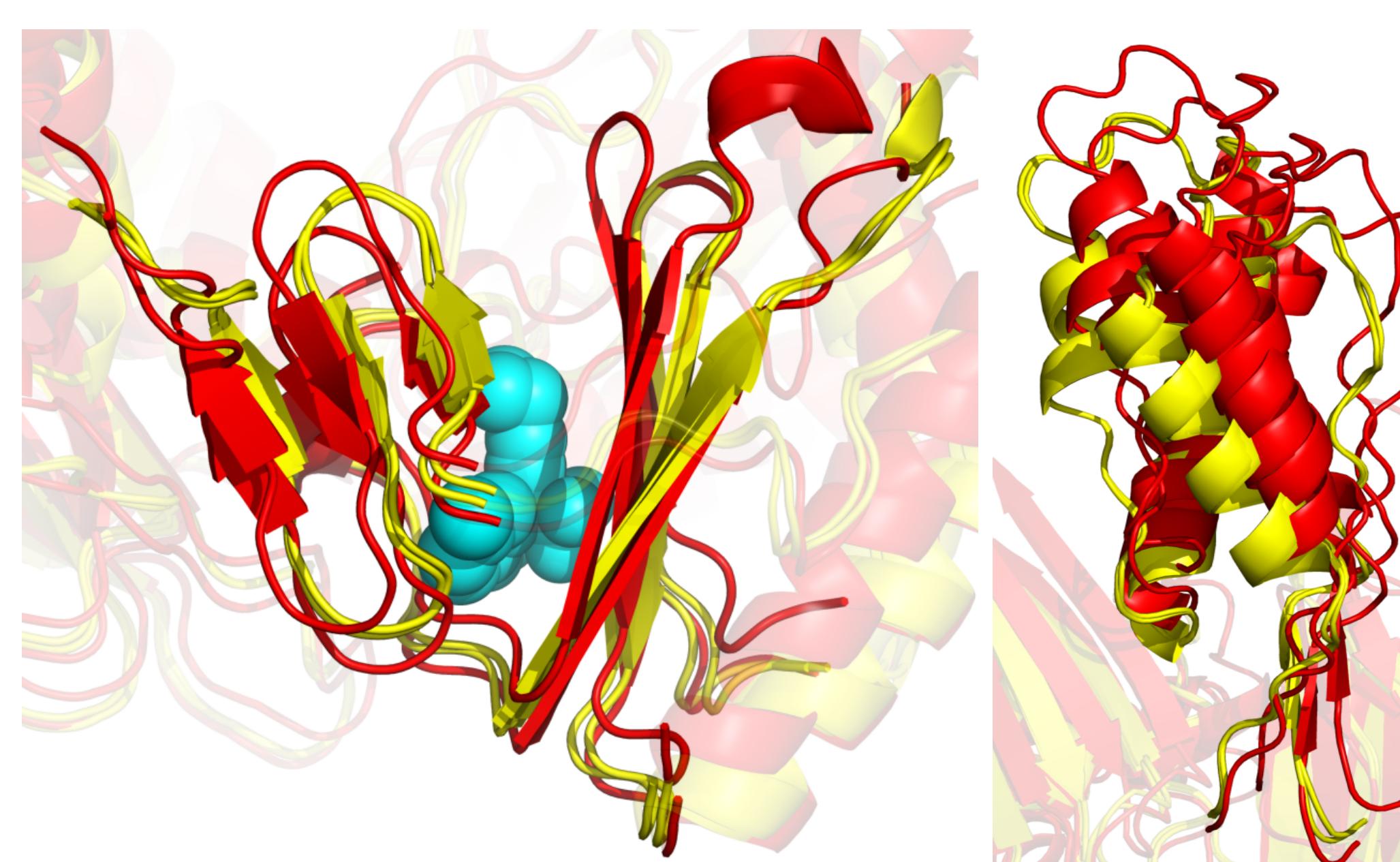
## Hierarchical Clustering



## Structural Differences are Subtle

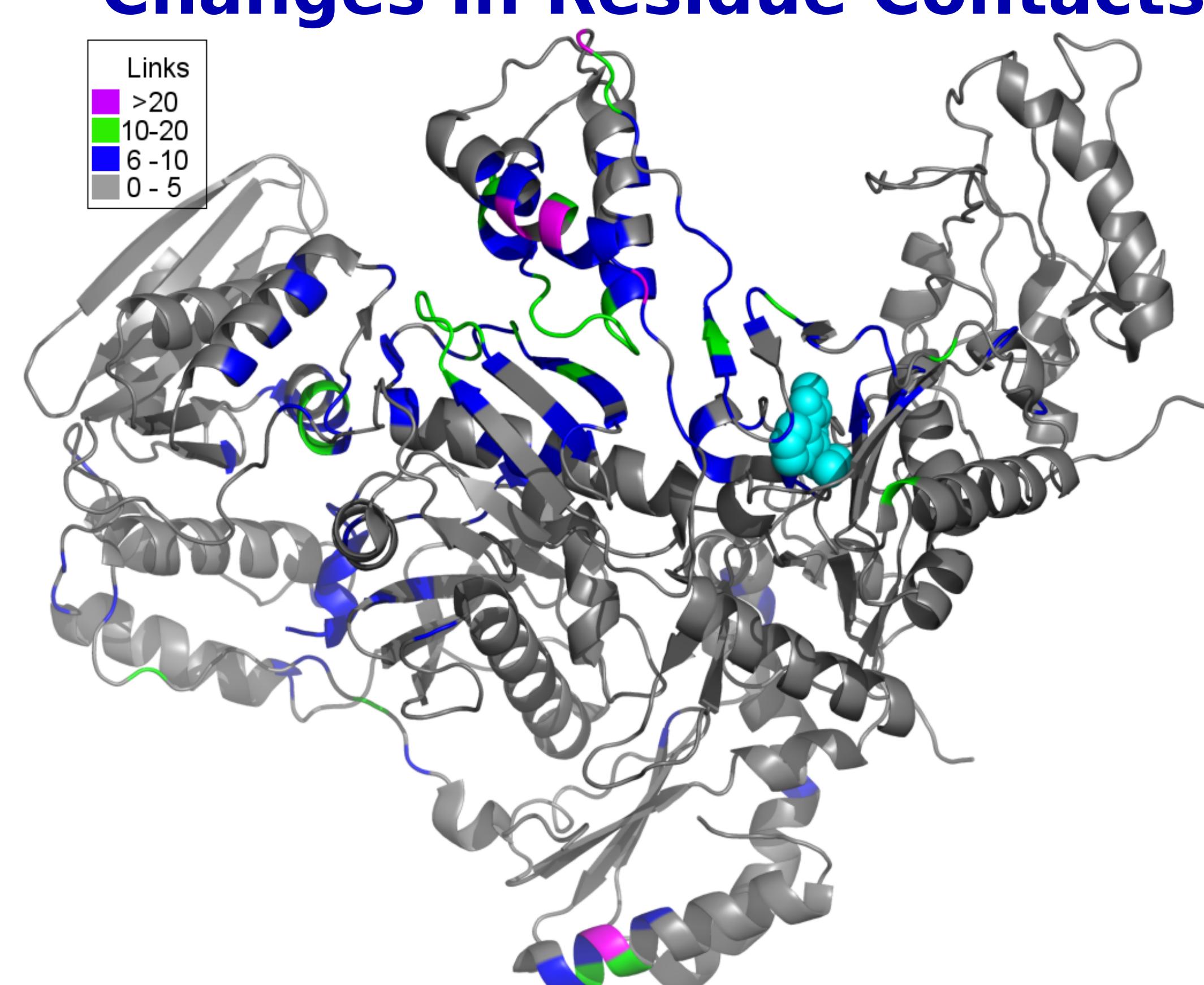


## Deformation of Drug Binding Pocket Alters Thumb Position



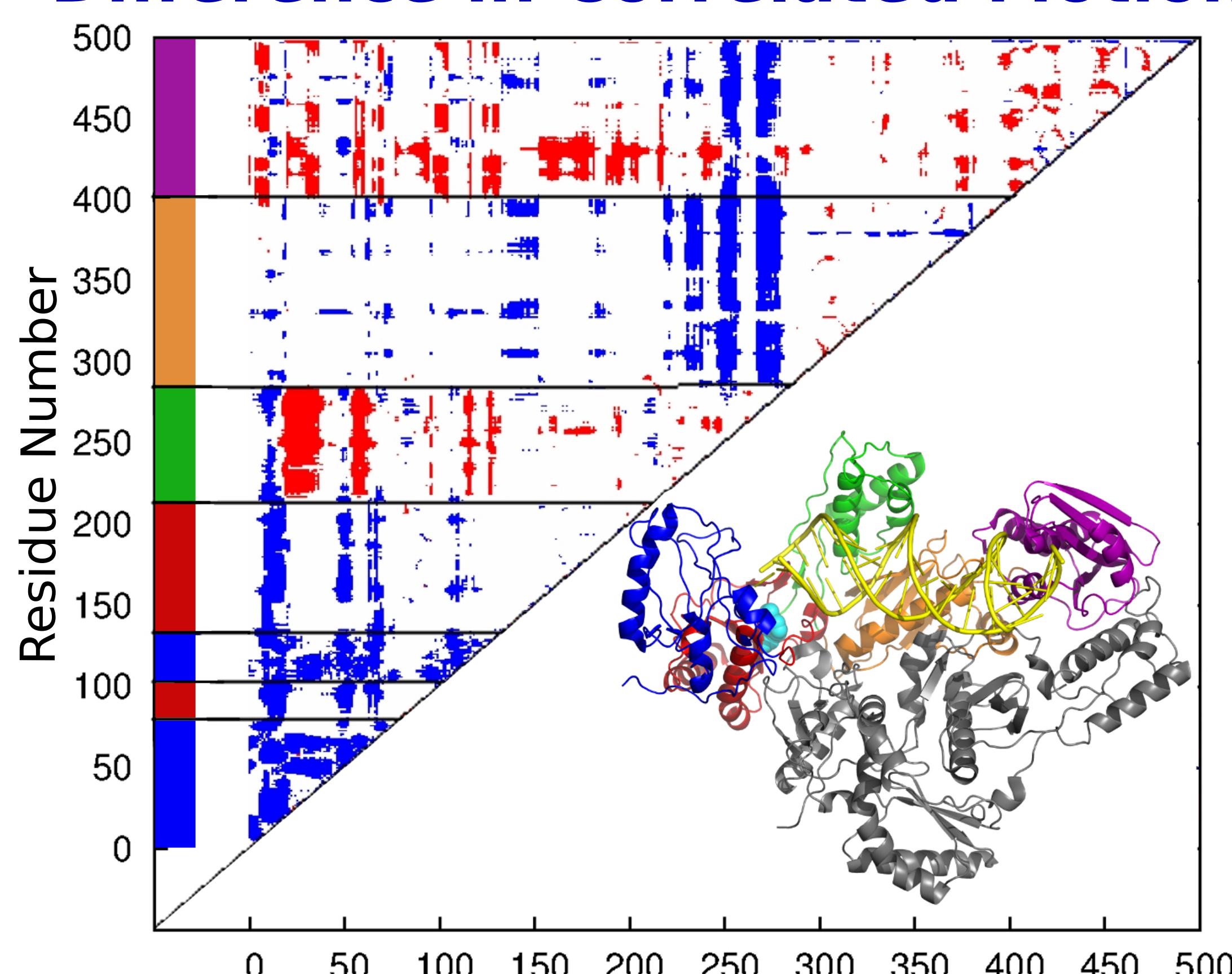
- Pre-active thumb subdomain lifts away from connection domain
- Inactive thumb subdomain rests directly against connection subdomain

## Changes in Residue Contacts



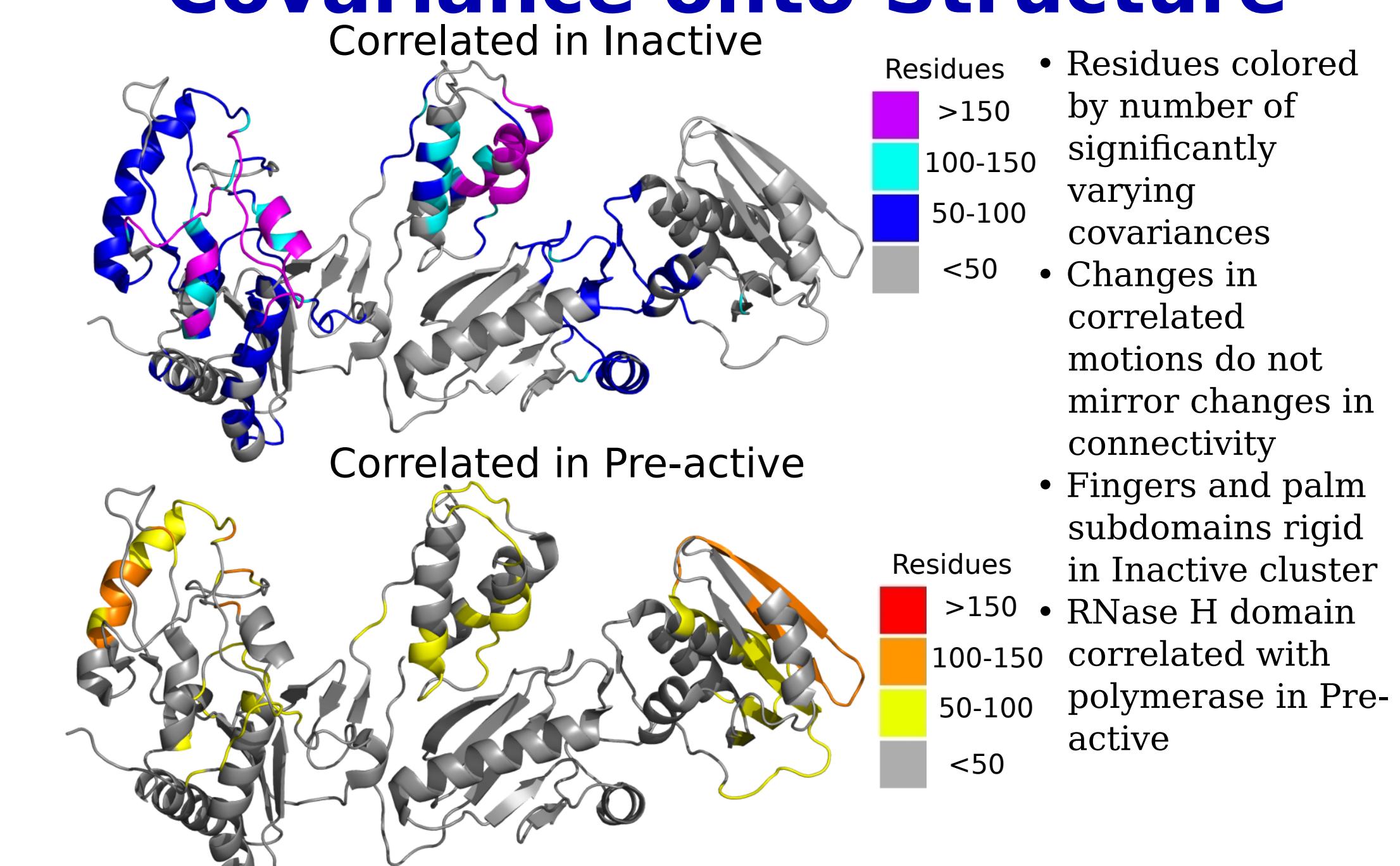
- ENMs insensitive to small changes in number of residue contacts
- Connectivity changes strongest in thumb subdomain
- Subtle structural changes lead to large connectivity changes
- Large connectivity changes lead to dynamics changes
- NNRTI (cyan)

## Difference in Correlated Motion



- Plot of significant differences in covariance between inactive and pre-active cluster
- Motion correlated in Inactive only (blue)
- Motion correlated in Pre-active only (red)

## Mapping Changes in Covariance onto Structure



- Dynamics and structure both require to characterize function
- Structures with similar function show a linear relationship between structure and dynamics
- MD not bioinformatics tool
- ENMs can be bioinformatics tools
- Subtle changes in structure can lead to larger changes in dynamics
- Hydrophobic core mutations cause a change in structure/dynamics
- Rotation of thumb
- Restores unliganded motions
- Small changes in structure can lead to distant changes in dynamics

Work done in LOOS (Lightweight Object Oriented Structure analysis library), an open source C++ library designed and maintained by the Grossfield lab. LOOS provides a concise, adaptable framework for designing analysis tools that interfaces with native file formats of most simulation packages.

<http://loos.sourceforge.net>

