Nussinov pioneered the “conformational selection and population shift” (1999) as an alternative to the “induced fit” text-book model to explain molecular mechanism of recognition and posited that population shift underlies allosteric regulation. She extended this pre-existing ensemble model to catalysis (2000), and oncogenic activation, contributing to extraordinary advancements in understanding structure and function.

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In the 1990s Nussinov proposed the model of “conformational selection and population shift” as an alternative to “induced fit” to explain molecular recognition. The concept that she introduced emphasized that all conformational states preexist, available for a range of ligands to bind, followed by re-equilibration (shift) of the ensemble. It also clarified how allosteric posttranslational modifications can work, and underscored that lipids, ions and water molecules can also act via allostery. This paradigm has impacted the scientific community's views and strategies in allosteric drug design, biomolecular engineering, molecular evolution and cell signaling. In line with Nussinov’s proposition, dynamic population shifts are now broadly recognized as the origin of allostery. It also explains the effects of allosteric, disease-related activating mutations. The new concepts that her group pioneered have changed the way biophysicists and structural biologists think about protein-ligand interactions and are now included in chemistry/biochemistry courses. The profound significance, and advance was also heralded in *Science* (320: 1429, 2008) as innovating on the decades-old concepts, noting that although textbooks have championed the induced fit mechanism for more than 50 years, data (especially NMR) unequivocally support the powerful paradigm for diverse biological processes. The conformational selection/population shift mechanism is now widely established. As Nussinov and others have shown, the new paradigm helps unravel processes as diverse as signaling, catalysis, gene regulation, and aggregation in amyloid diseases, and recently, the mechanisms of activating mutations in oncogenic Ras, its effectors and downstream pathways, establishing the molecular mechanism of PI3K activation, and clarifying inhibition scenarios.