LEVERAGING CONFORMATIONAL HETEROGENEITY IN PROTEINS FOR DRUG DISCOVERY

Adrian Velazquez-Campoy[1,2,3,4], David Ortega-Alarcon[1,2], Paula María Garcia-Franco[1,5], Marta Asencio del Rio[1,2], Hajar Jeblaoui[1,2], Francisco Javier Falcó-Martí[1,2], Gema Merino-Loma[1,2], Sonia Vega[1], Juan José Galano-Frutos[1,5], Olga Abian[1,2,3,4]

[1] Institute of Biocomputation and Physics of Complex Systems (BIFI), Universidad de Zaragoza, 50018 Zaragoza, Spain
[2] Aragon Health Research Institute (IIS Aragon), 50009 Zaragoza, Spain
[3] Networking Biomedical Research Centre in Liver and Digestive Diseases (CIBEREHD), 28029 Madrid, Spain
[4] Department of Biochemistry and Molecular and Cell Biology, University of Zaragoza, 50009 Zaragoza, Spain
[5] Certest Biotec S.L., 50840 San Mateo de Gallego, Zaragoza, Spain

adrianvc@unizar.es

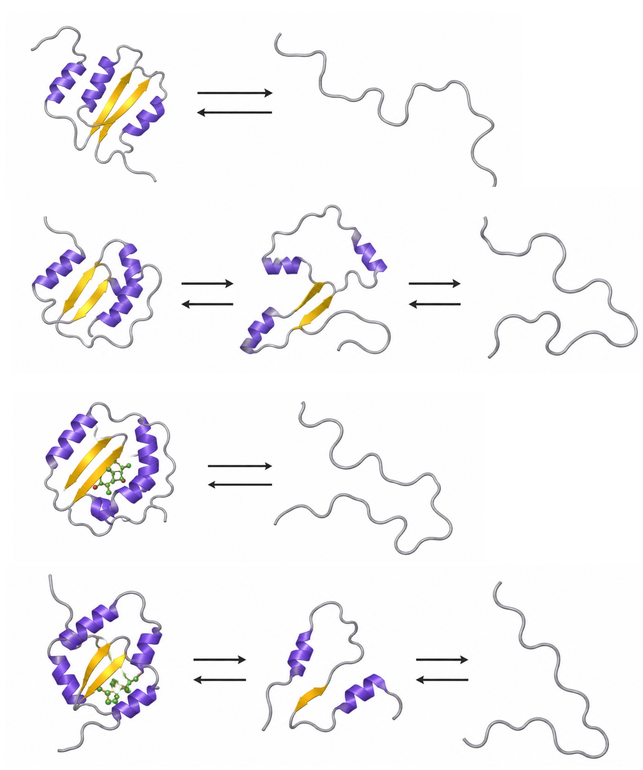
1. Abstract

Due to the emergence of new diseases, unmet medical needs or orphan diseases, as well as the reduced efficacy of certain therapeutic agents, there is an urgent need for new drugs that act on new targets and/or via new mechanisms.

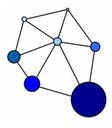
Proteins can adopt several macroscopically distinguishable conformations, the populations of which are governed by their intrinsic structural stability and the interaction of different biological effectors (cofactors, activators and inhibitors, interactors) and environmental variables, giving rise to macromolecular ensembles in which certain conformational states may be physiologically and/or pathologically relevant.

This is particularly relevant in the case of intrinsically or conditionally disordered proteins. Transient, non-native alternative conformational states may be the target of drugs that stabilize these states and prevent conversion to functional active states in an allosteric manner, thereby blocking the activity of disease-related dysregulated proteins.

2. Conformational Heterogeneity in Proteins

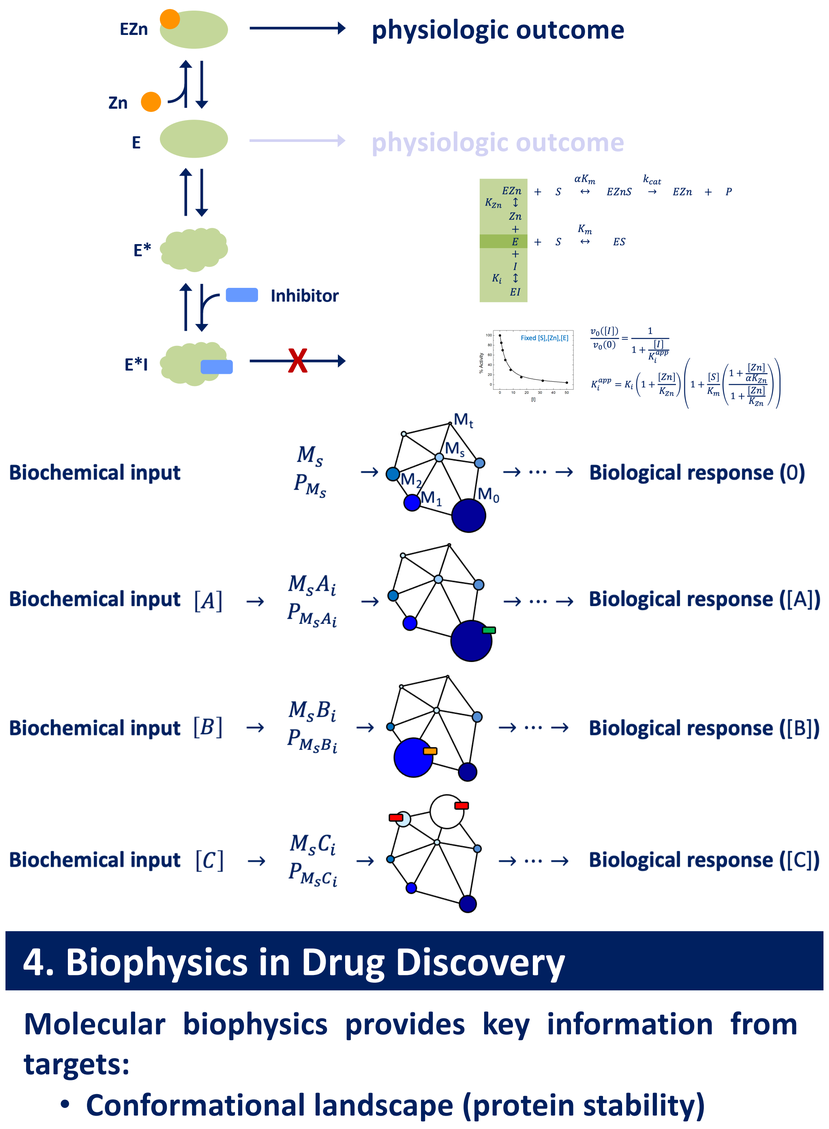


- Well-folded proteins
- Conditionally disordered proteins
- Intrinsically disordered proteins
- Simple and complex proteins



3. Conformational States as Targets

Compounds binding and stabilizing alternative non-native states will act as allosteric ligands blocking the activity of the protein. These compounds may bind at the active site or at other sites (exosites).



4. Biophysics in Drug Discovery

Molecular biophysics provides key information from targets:

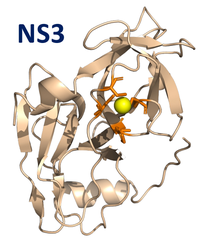
- Conformational landscape (protein stability)
- Functional landscape (conformation-interaction coupling)
- Interactions with biological partners
- Influence of environmental parameters
- Effect of clinically relevant mutations (structure & function)
- Sites and modes of interaction

Biophysics can be employed in drug discovery for:

- Selection of target variant
- Identification of weaknesses and key features in protein target
- Selection of experimental conditions
- Design of HTS procedure (assay development)
- Validation of screening procedure
- Confirmation of target engagement for hits/leads

5. Drug Targets at BIFI-LACRIMA

NS3

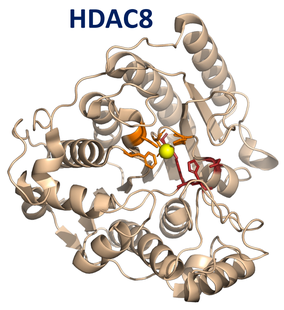


NS3 protease from hepatitis C virus
Hepatitis C and hepatocarcinoma

BFT-3

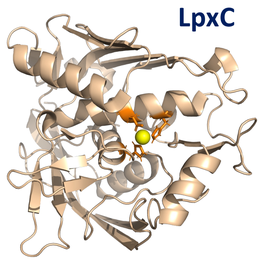
Bacteroides fragilis toxin
Chronic inflammation and colorectal cancer

HDAC8



HDAC8 deacetylase
Cancer and neurological disorders

LpxC

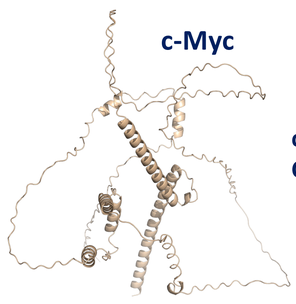


LpxC bacterial deacetylase
MDR Gram-negative bacterial infections

MeCP2

Methyl-CpG binding protein 2
Rett syndrome and cancer

c-Myc



c-MYC and n-MYC
Cancer

Grants PID2024-160408OB-I00, PID2021-127296OB-I00, and BFU2016-78232-P funded by MICIU/AEI /10.13039/501100011033 and by FEDER, UE
LA-3: Plataforma de cribado de fármacos y análisis de interacciones fármaco-diana (Plan Complementario en Biotecnología Aplicada a la Salud) funded by (NextGenerationEU and Plan de Recuperación, Transformación y Resiliencia (PRTR-C17.I1))