Computational modelling of protein dynamics in heart disease

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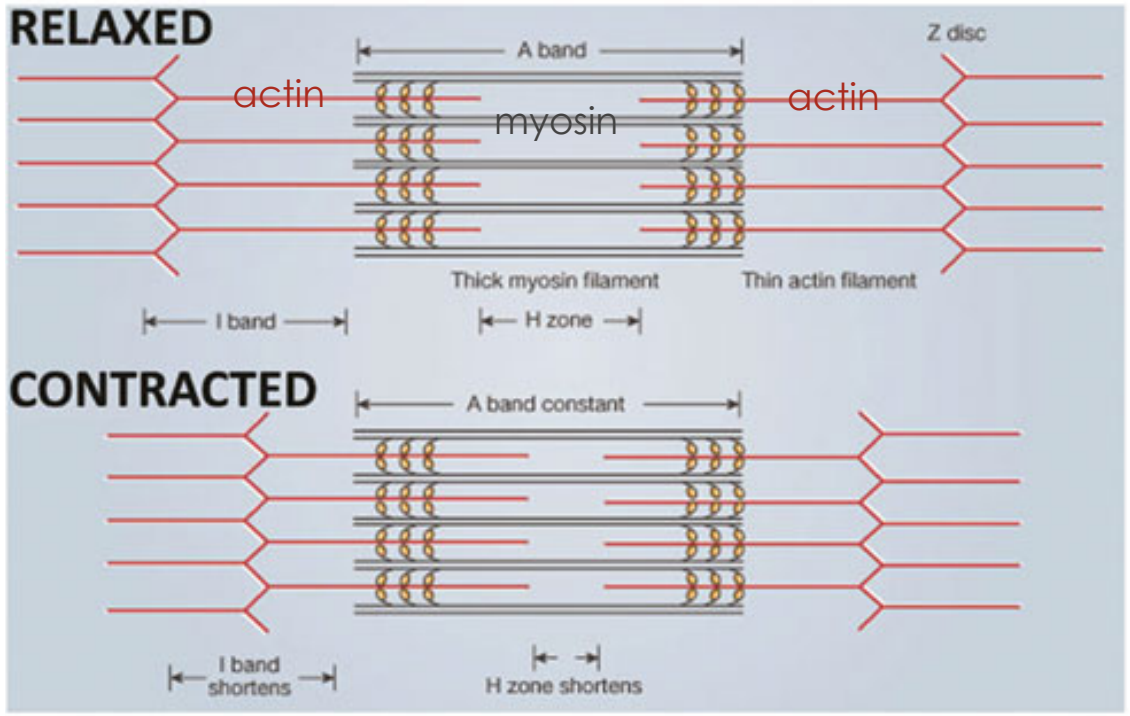
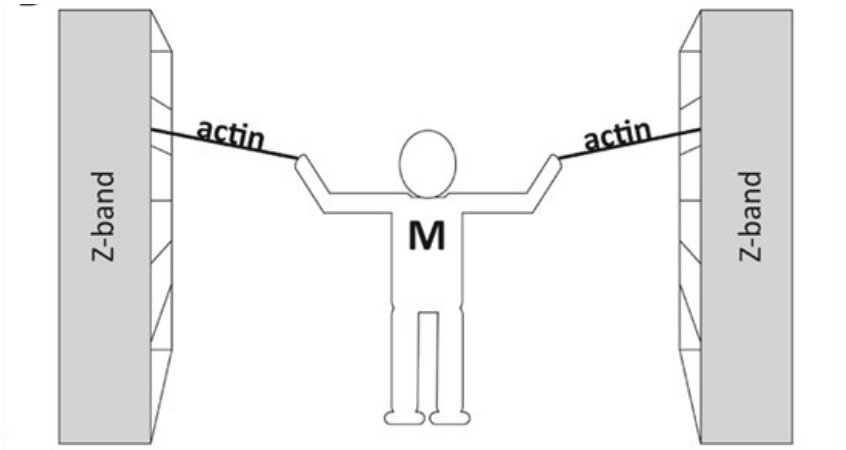
Queen Mary University of London

Powering Up Research – 13 Nov 2017

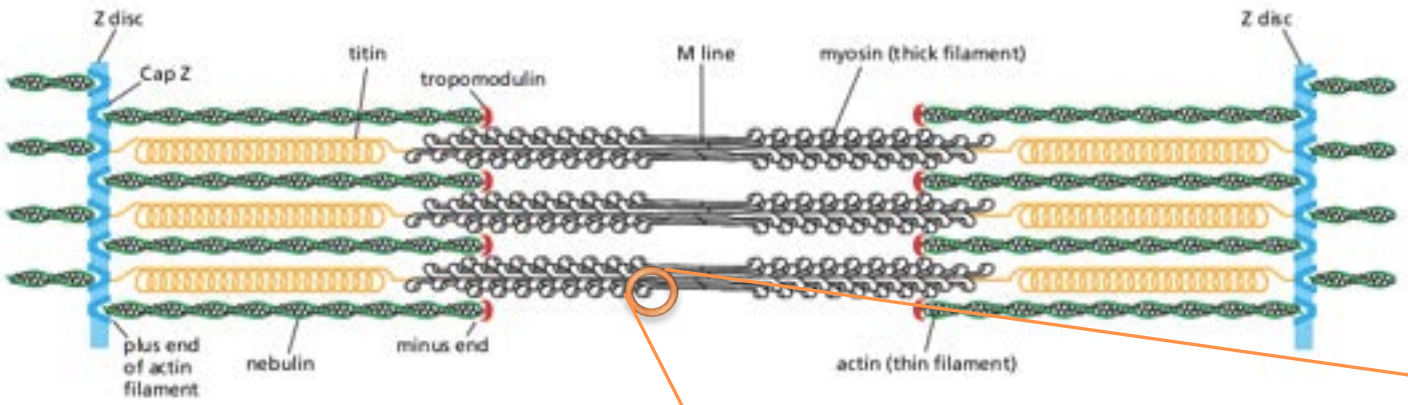
Muscle contraction



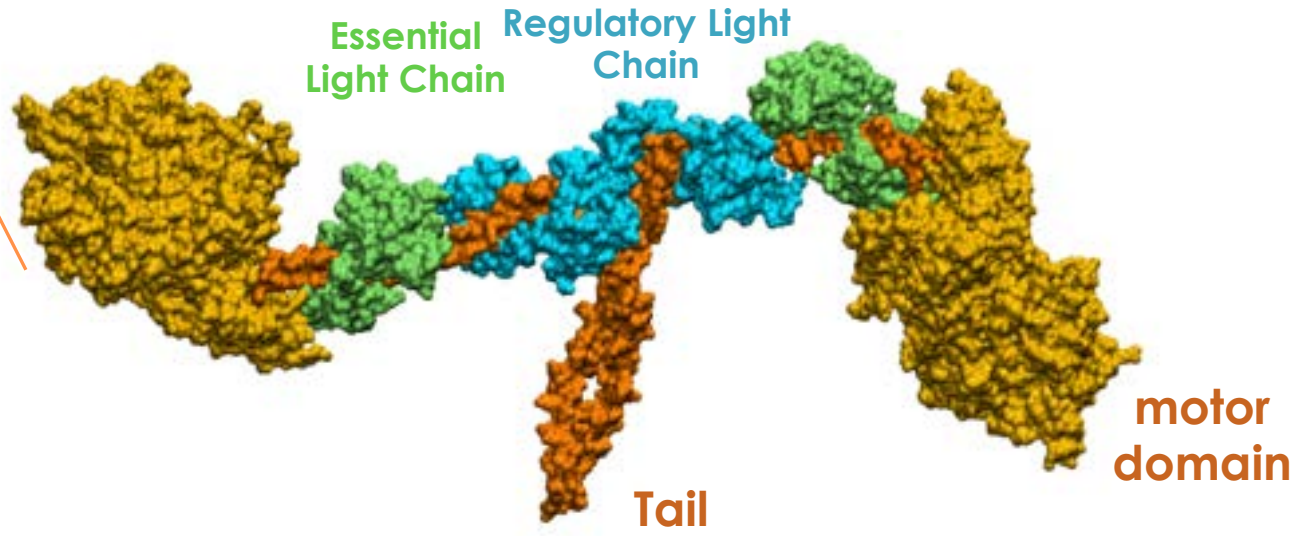


Krans, J. L. (2010) Nature Education 3(9):66

Myosin and the Sarcomere



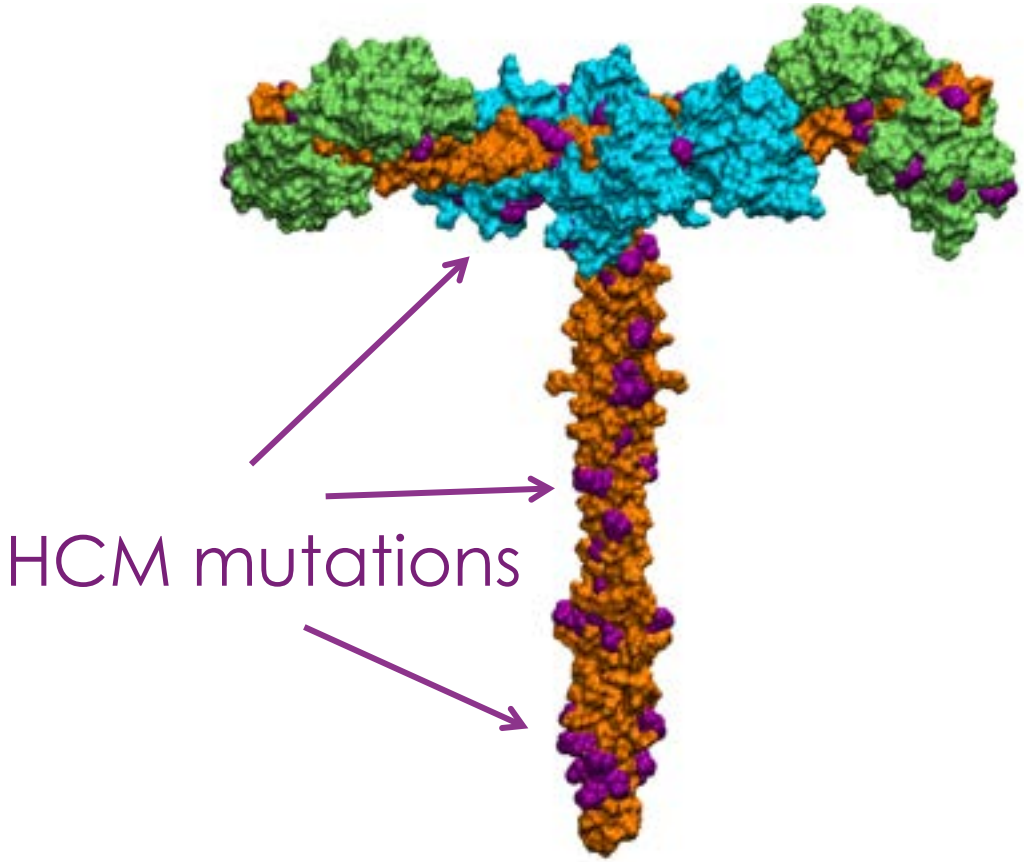
Alberts et al., Molecular Biology of the Cell, 2008



Myosin dynamics

- Essential for muscle contraction
- Can be regulated by chemical modifications (normal conditions)
- Can be disrupted by genetic mutations (pathological conditions)

Cardiac myosin and genetic mutations



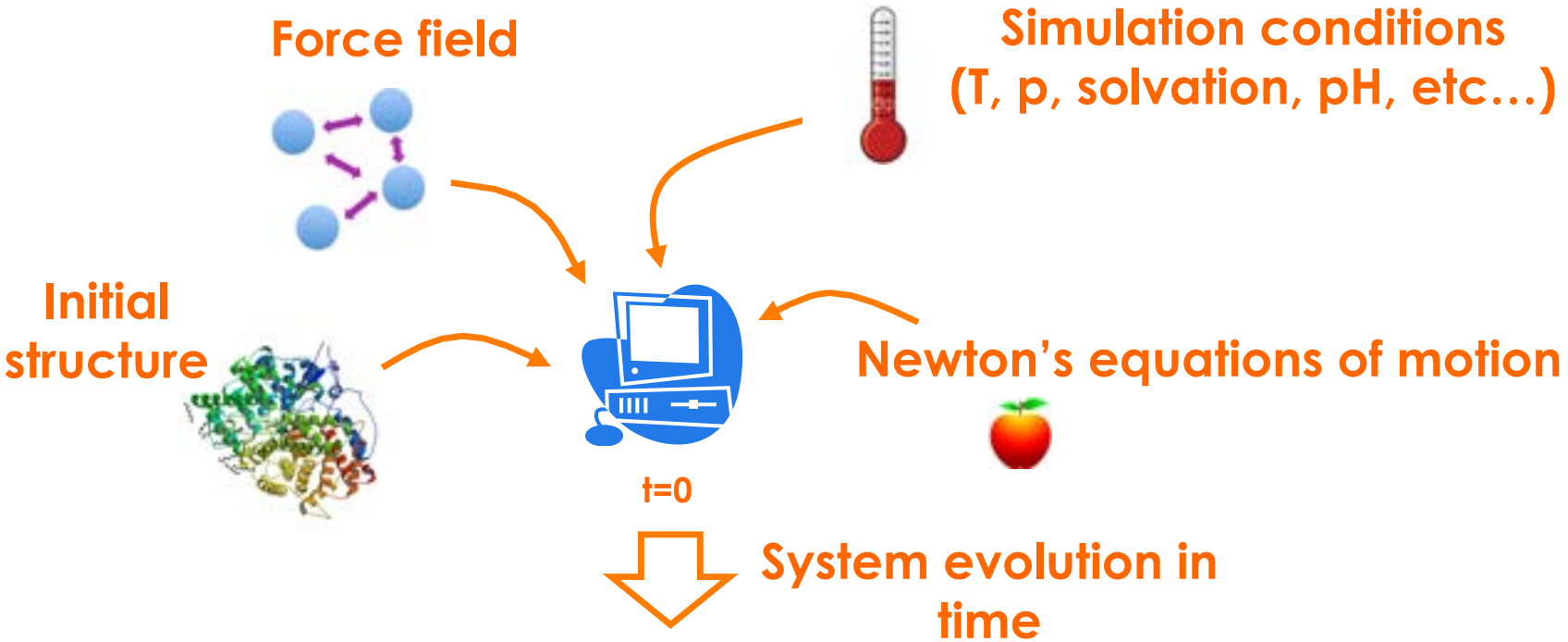
Myosin contains hundreds of genetic mutations related to heart disease (in part. hypertrophic and dilated cardiomyopathy)

Study of myosin dynamics

- Provides information on myosin under normal and pathological conditions
- Can be used to develop therapies for the treatment of cardiac diseases
- Difficult to do with experimental techniques

Molecular Modelling and Simulation!

Molecular Dynamics Simulations



Molecular Dynamics – Time Scale

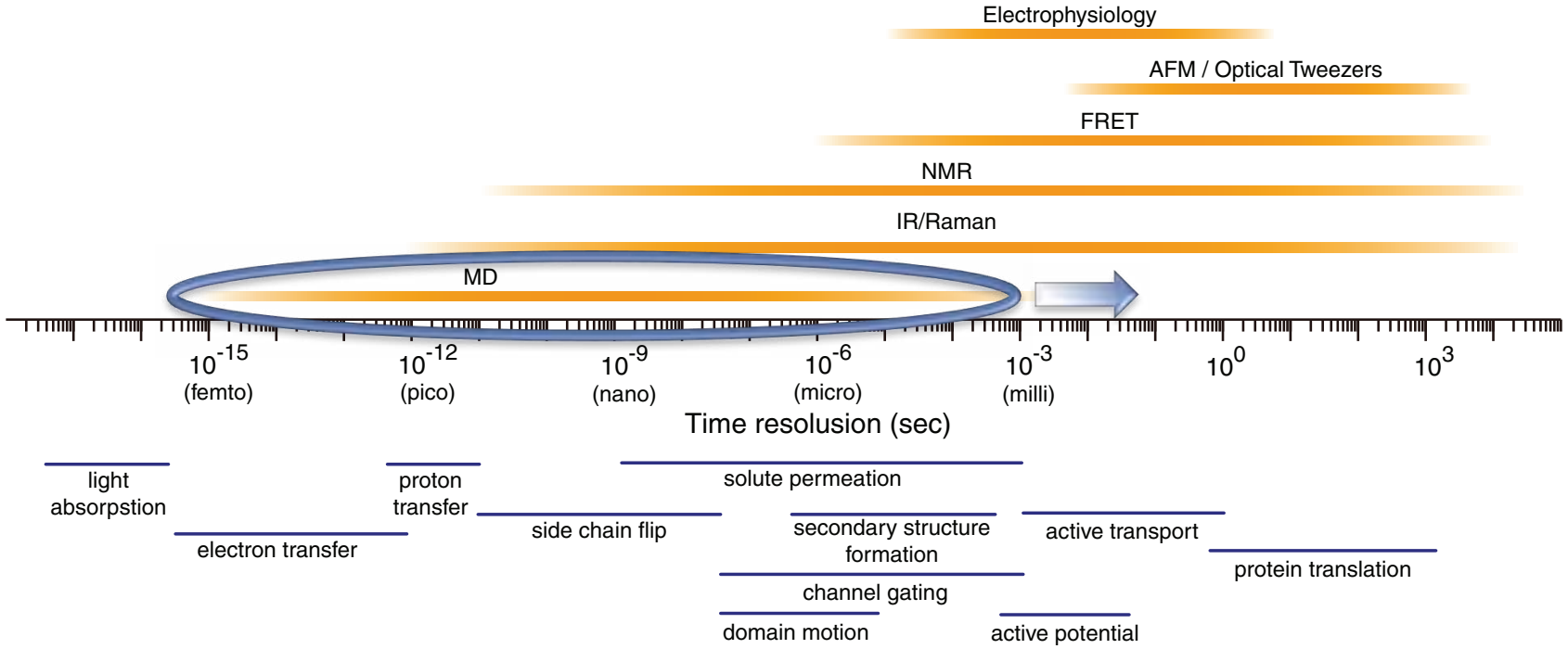


FIGURE 1 | Temporal resolution of various biophysical techniques. The timescales of some fundamental atom- or molecule-scale motions are shown below. AFM, atomic force microscopy; FRET, fluorescence resonance energy transfer; IR, infrared radiation; NMR, nuclear magnetic resonance.

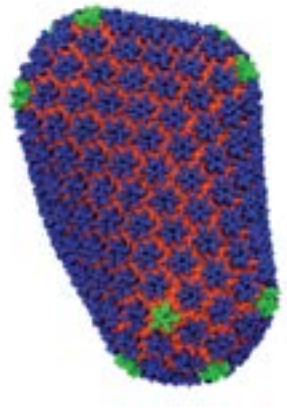
Ode, H., Nakashima, M., Kitamura, S., Sugiura, W. & Sato, H. *Front Microbiol* **3,** 258 (2012).

Molecular Dynamics – Size Scale

single protein in water

10-100k atoms

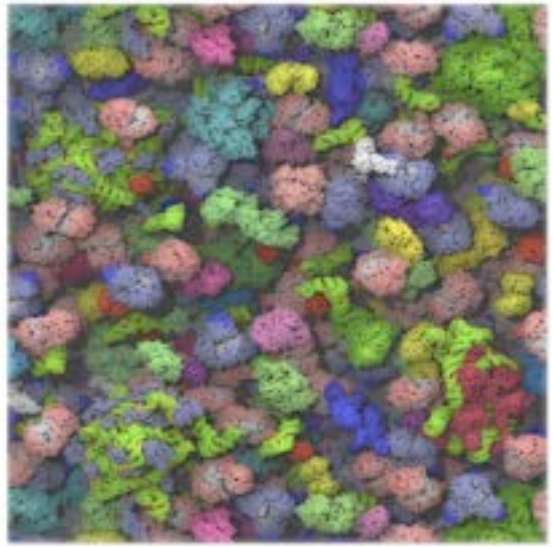
HIV-1 virus capsid



64 millions atoms

Zhao, G. *et al. Nature* **497**, 643 (2013)

E. coli cytoplasm

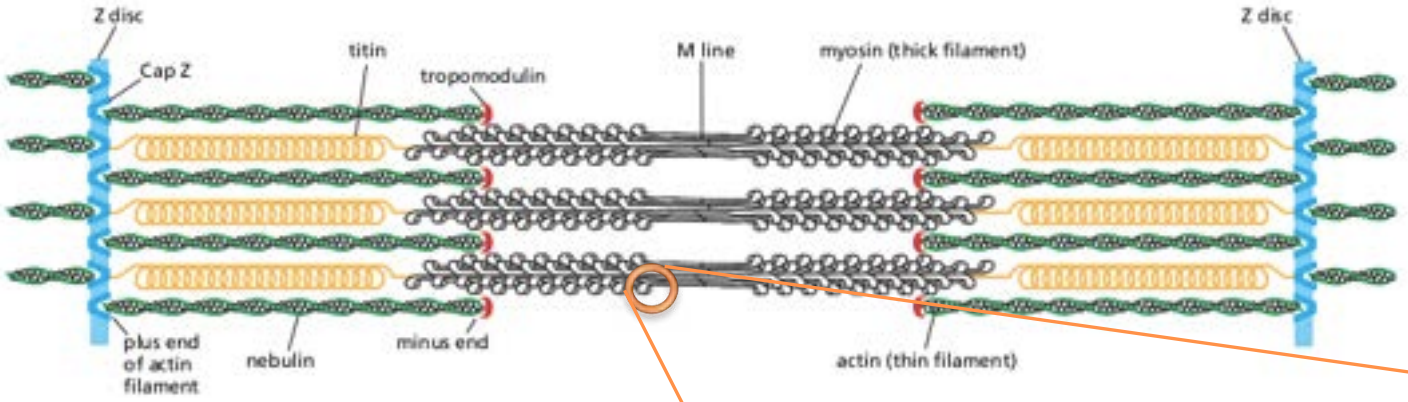


1008 molecules

McGuffee, S. R. & Elcock, A. H. *PLoS Comput Biol* **6**, e1000694 (2010).

system size

MD study of cardiac myosin



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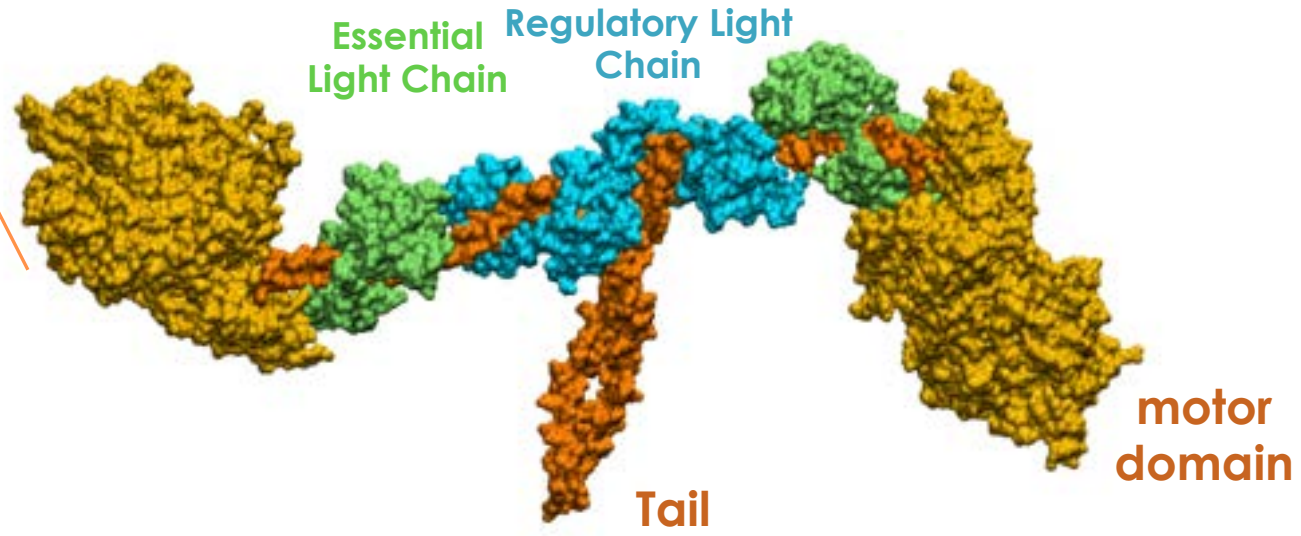
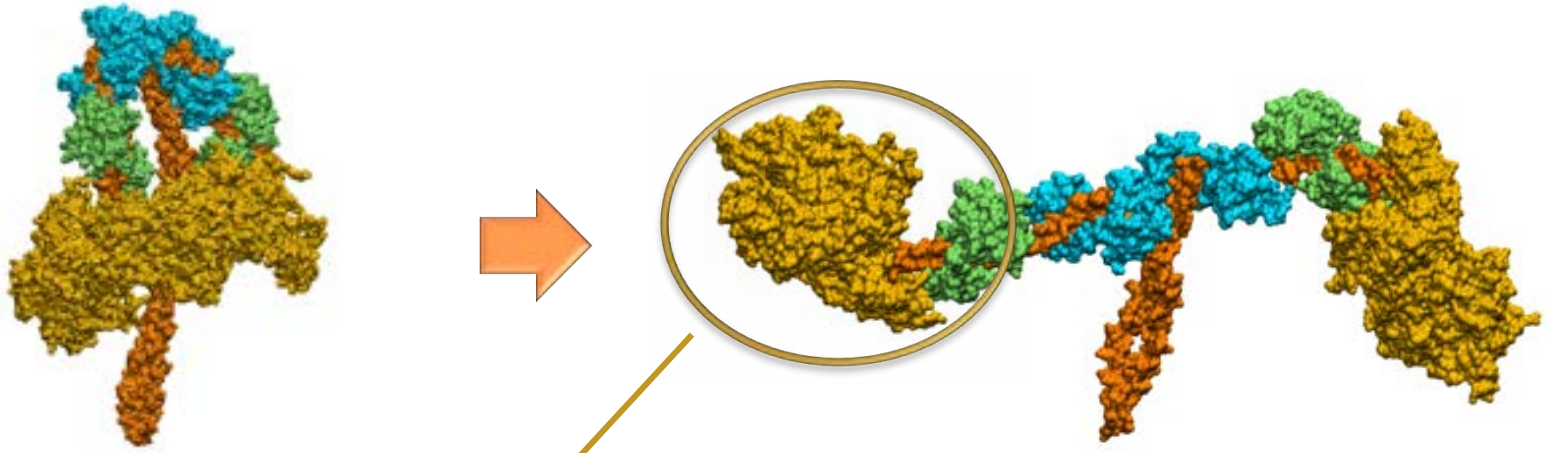
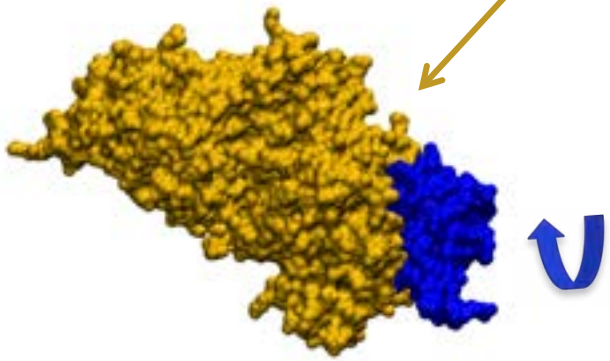


MD study of cardiac myosin

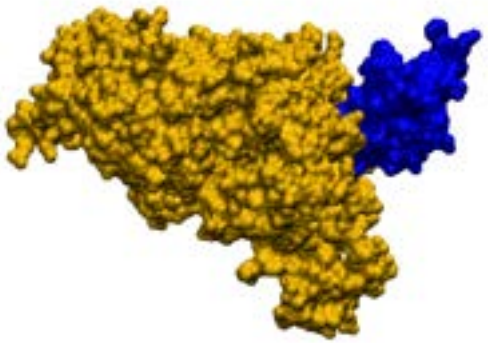
Off-On transition
(two heads)



Single head motion



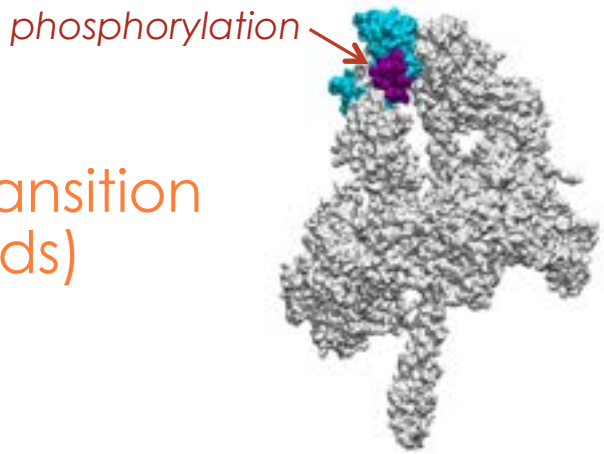
power stroke

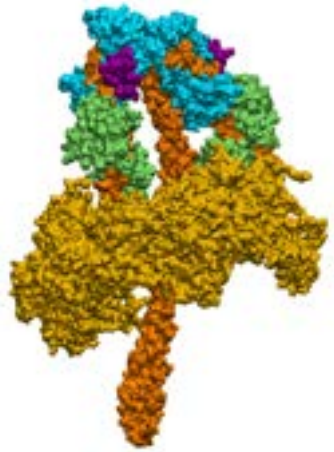


converter

MD study of cardiac myosin

Off-On transition
(two heads)

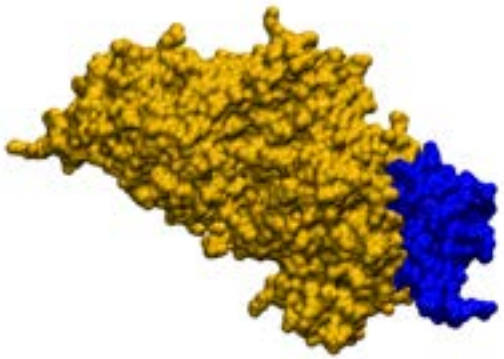




1. Dynamics of RLC

2. Dynamics of two-headed junction
(effect of genetic mutations)

Single head motion



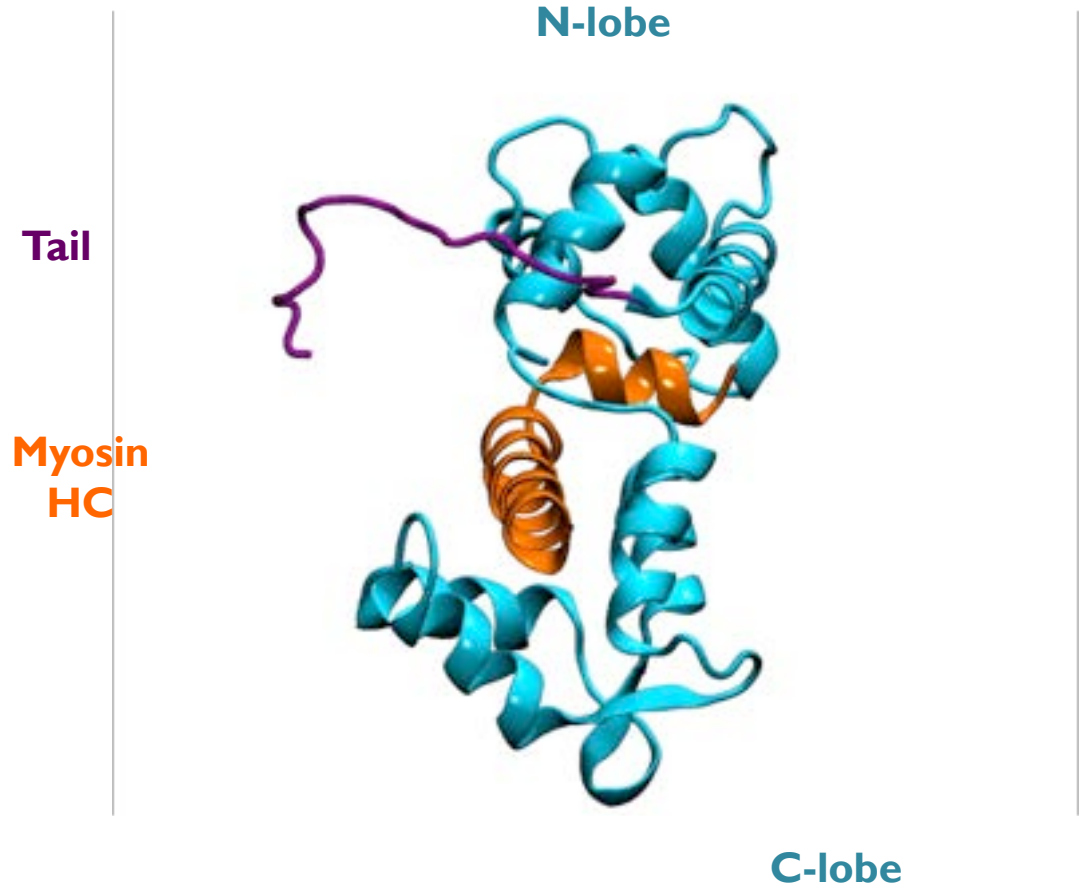
3. Effect of drug binding on myosin
dynamics

1. Dynamics of RLC

Contacts with RLC N-lobe

Contacts with RLC C-lobe

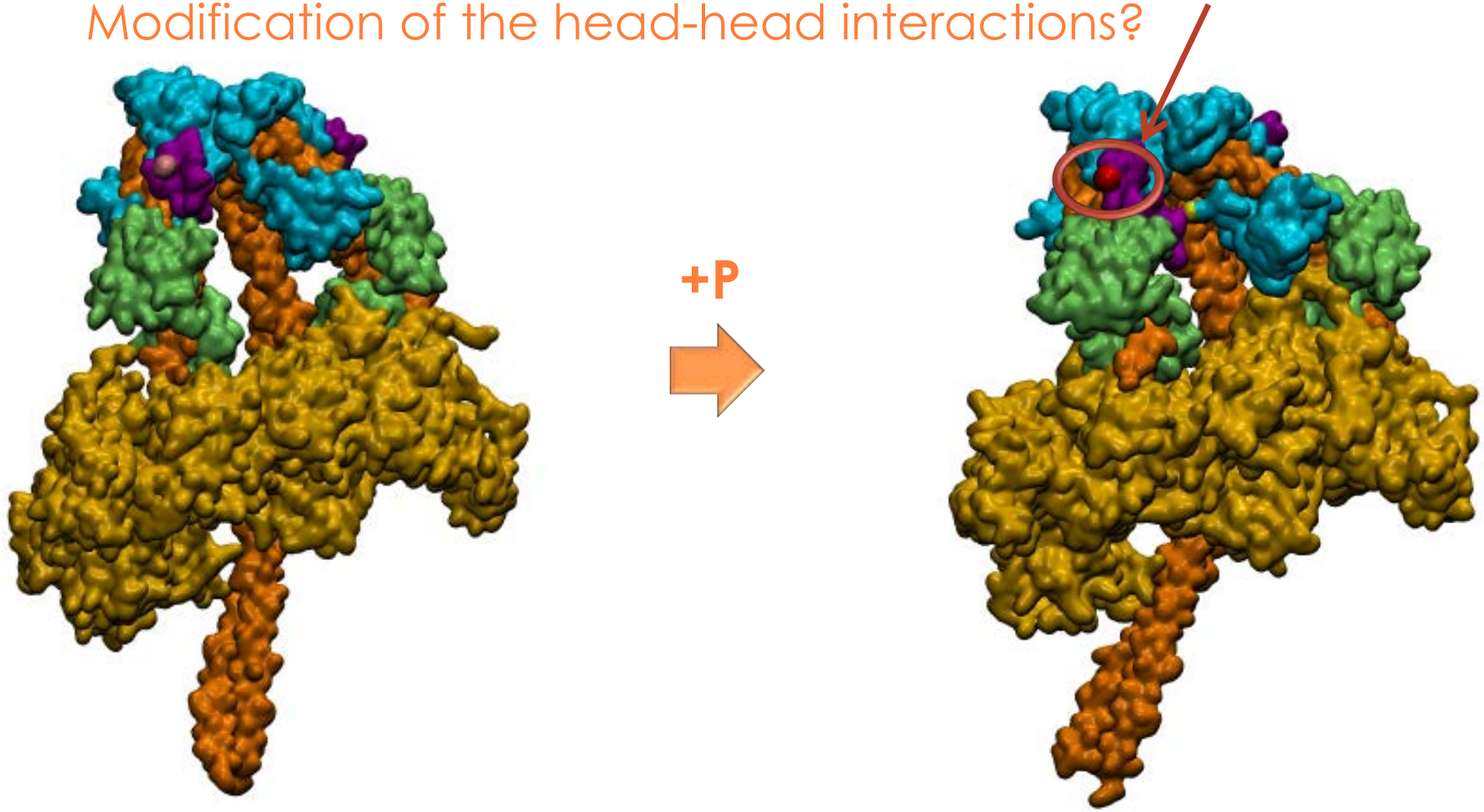
Contacts with Myosin HC



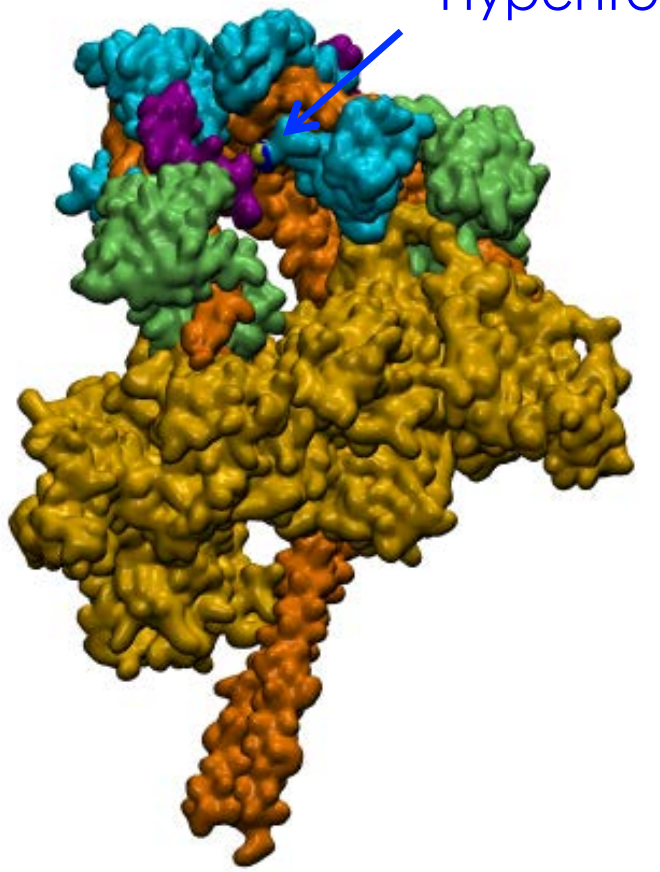
A. Fornili, E. Rostkova, F. Fraternali, M. Pfuhl: Biophysical J. 106 (2014) 33A.

2. Two-headed junction

Modification of the head-head interactions?

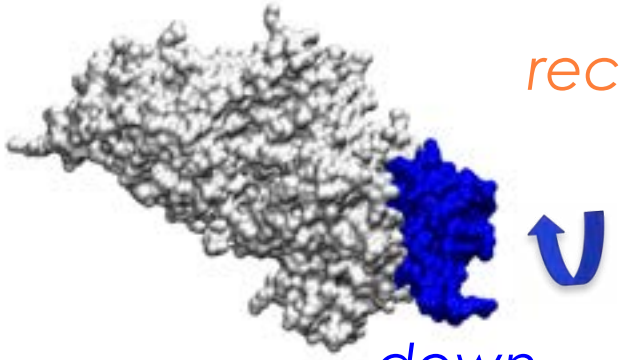


2. Two-headed junction

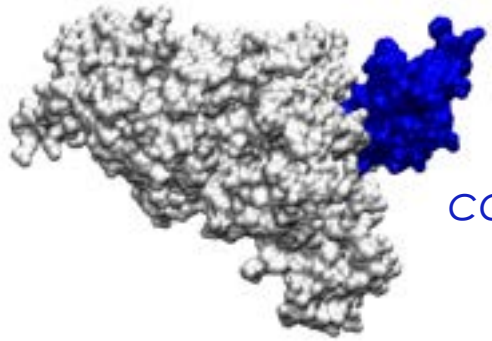


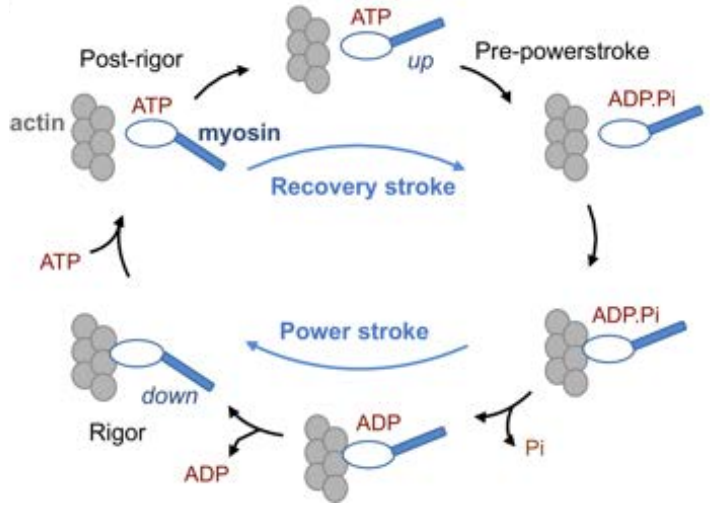
3. Effect of drugs

Single head motion

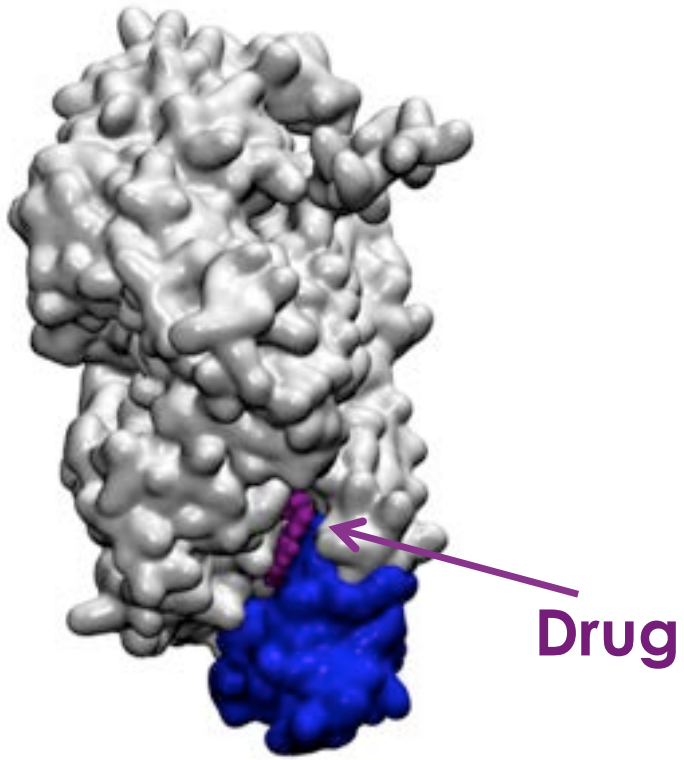


recovery stroke





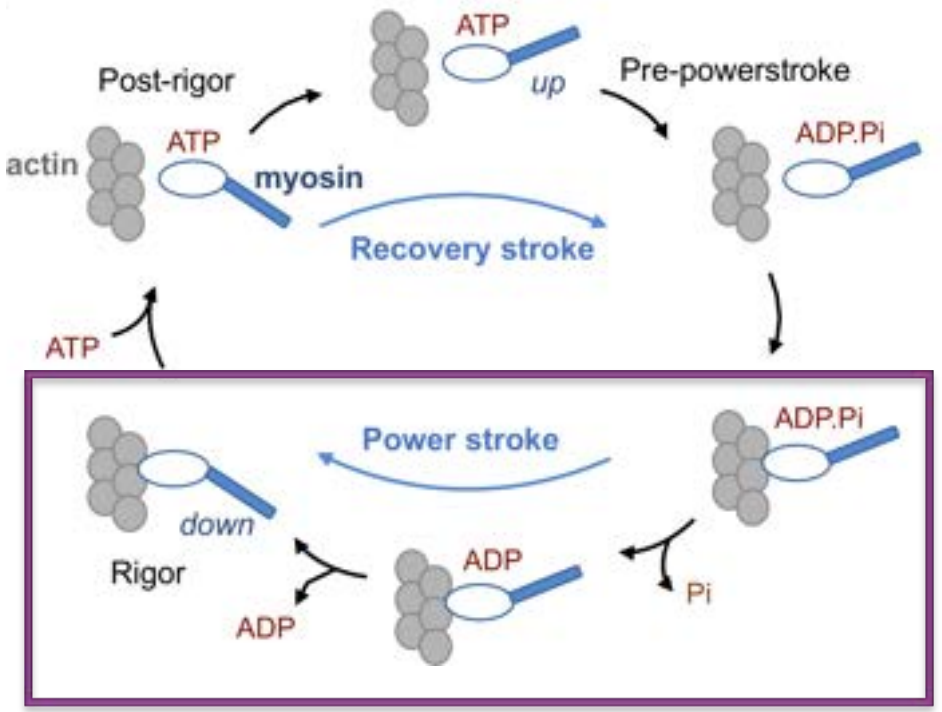
3. Effect of drugs



Omecamtiv mecarbil (OM)

- Increases the contractility of the heart muscle
- Currently in clinical trials for the treatment of heart failure
- Mechanism non fully understood

3. Effect of drugs

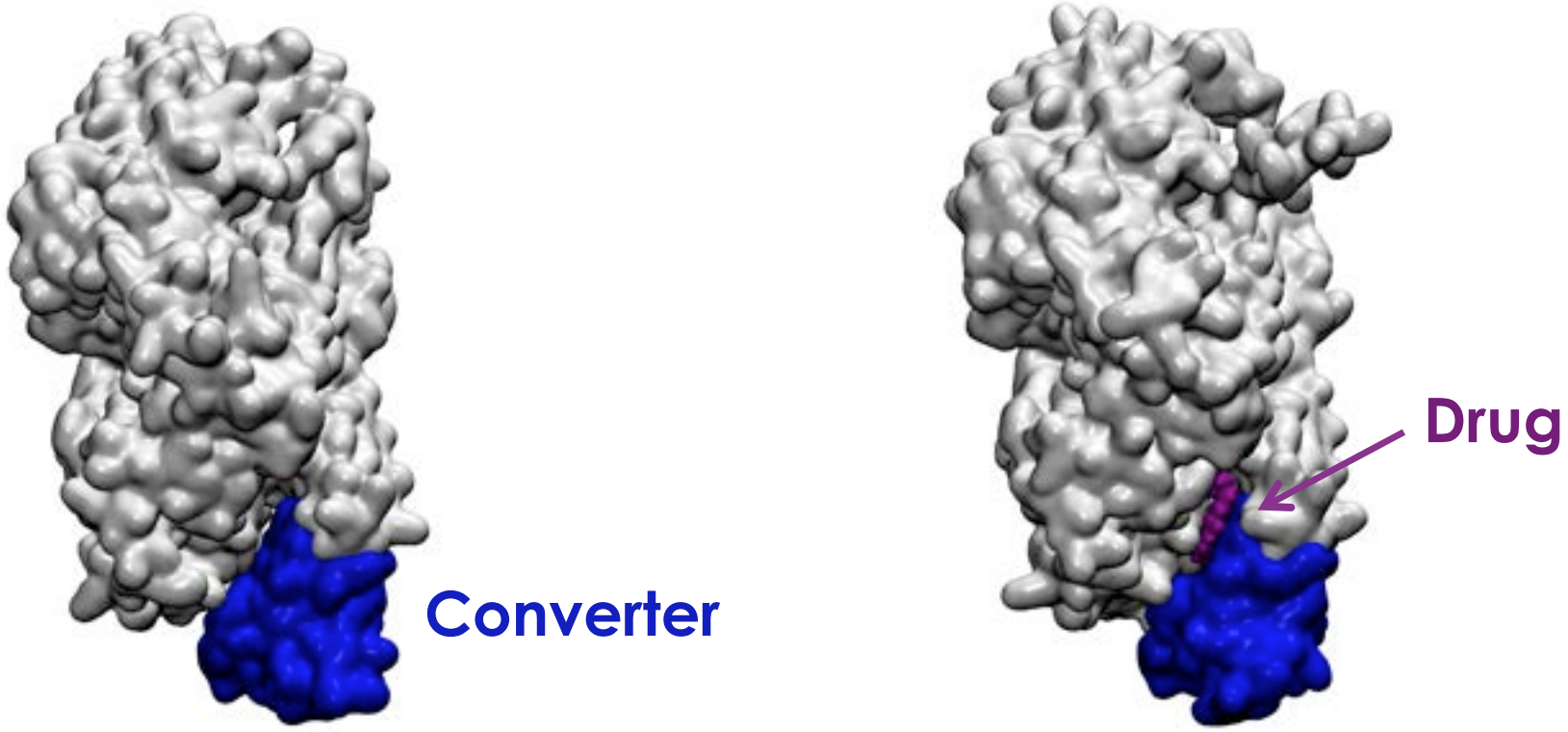


Omecamtiv mecarbil (OM)

- Increases the number of myosin molecules strongly bound to actin
- Slows down the power stroke

3. Effect of drugs

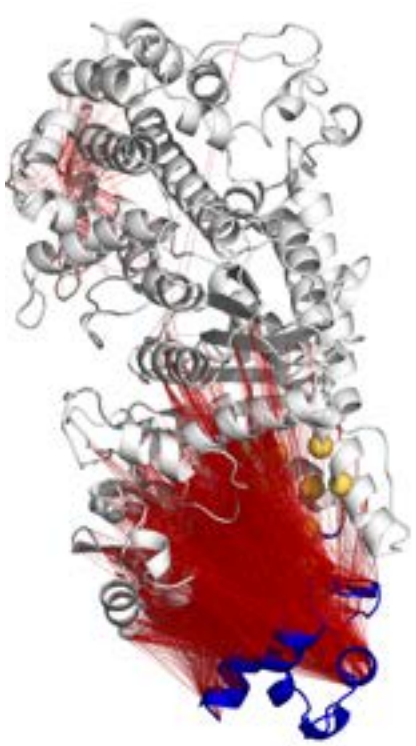
Is OM having any effect on myosin dynamics?



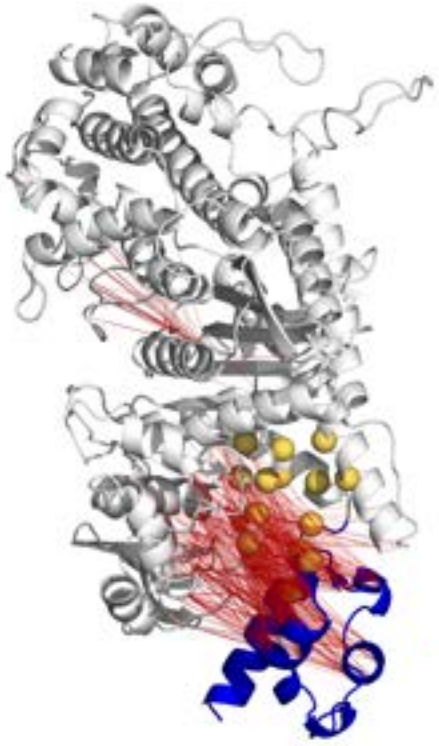
S. Hashem, M.Tiberti, A. Fornili, (2017) PLoS Comput Biol13(11): e1005826.

3. Effect of drugs

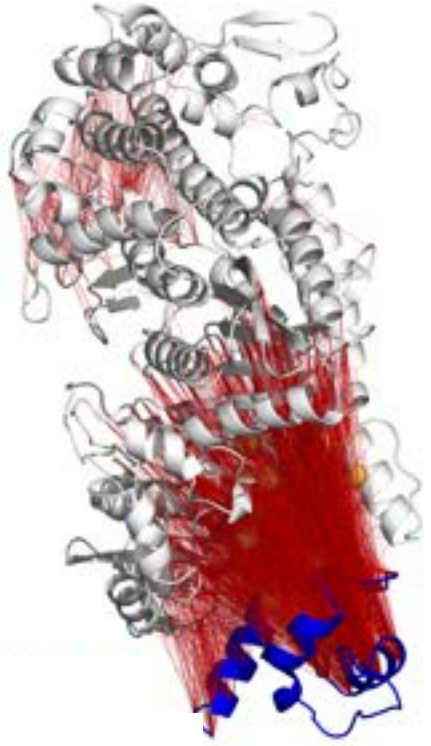
Replica 1



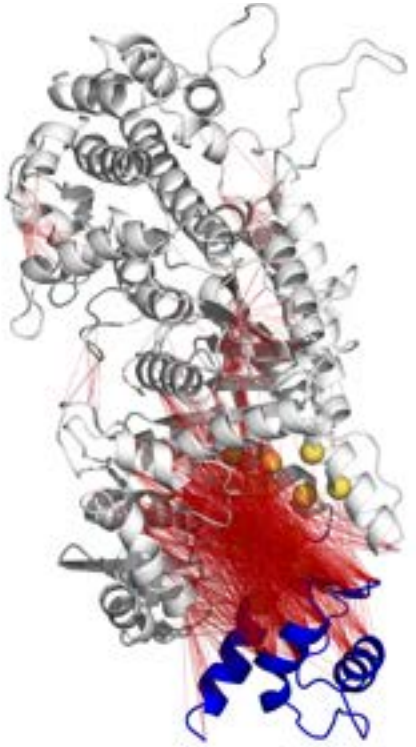
Replica 2



Replica 3



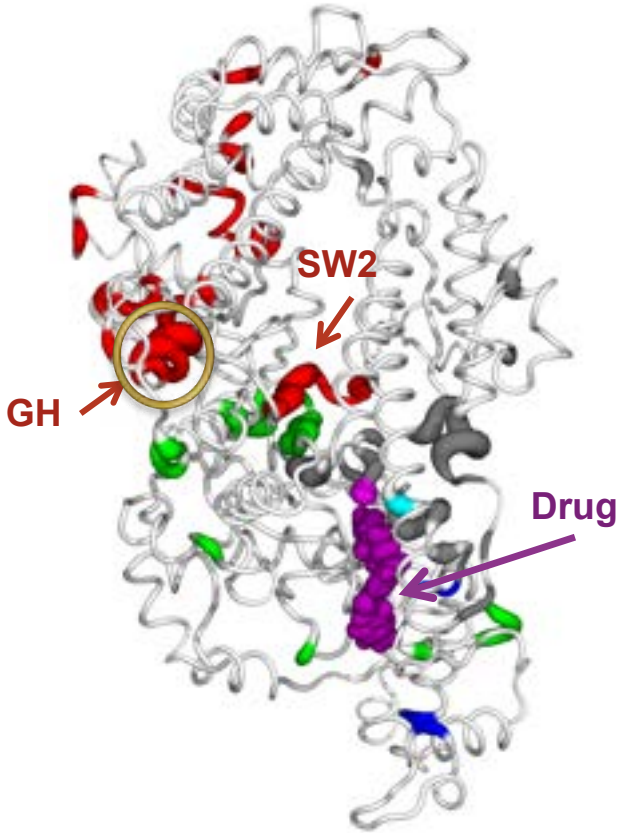
Replica 4

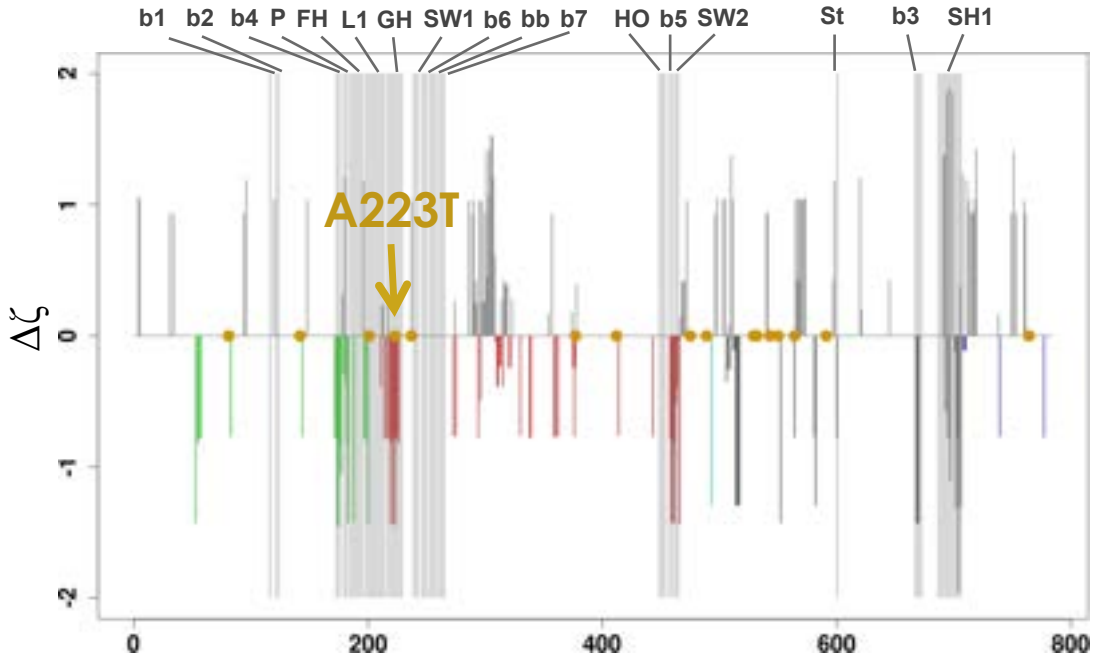


S. Hashem, M.Tiberti, A. Fornili, (2017) PLoS Comput Biol13(11): e1005826.

3. Effect of drugs

Preferential connection to the drug binding site

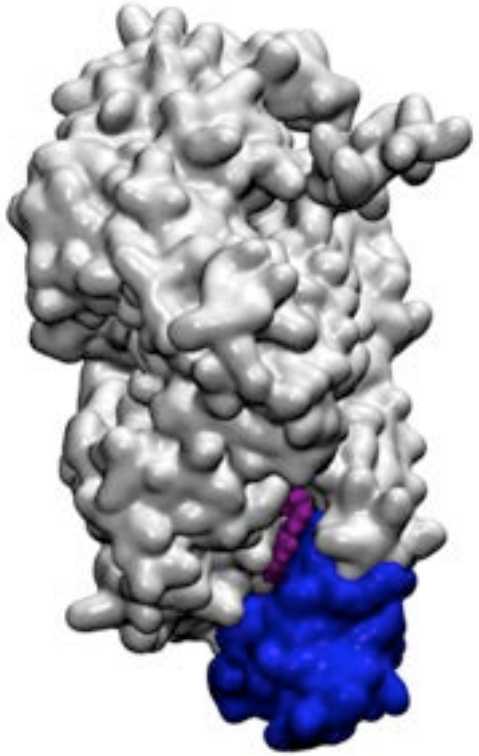




● = dilated cardiomyopathy mutations

S. Hashem, M.Tiberti, A. Fornili, (2017) PLoS Comput Biol13(11): e1005826.

3. Effect of drugs

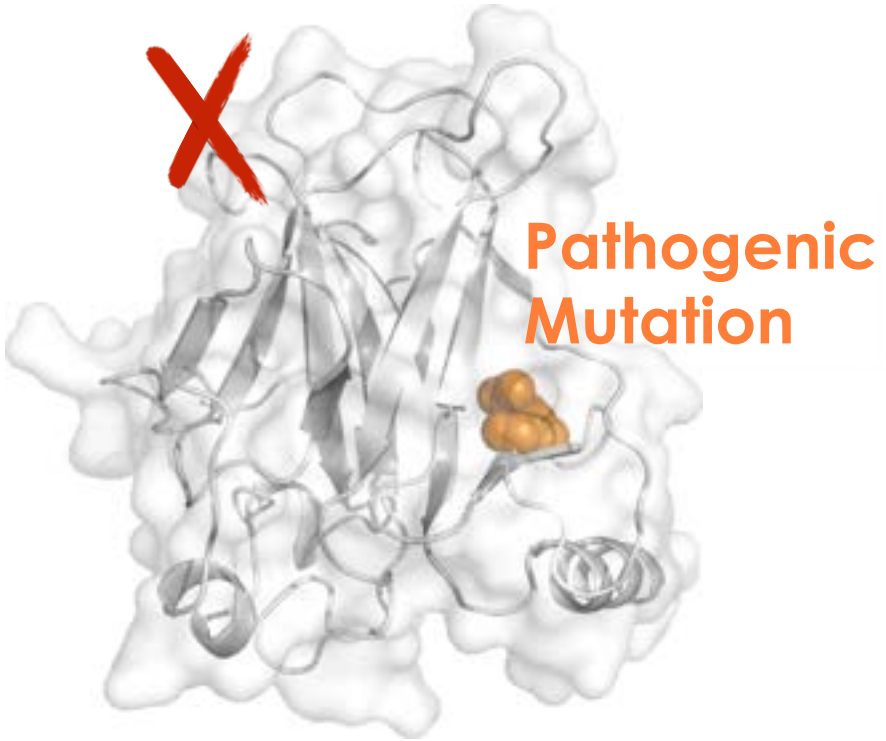


Conclusions from simulations:

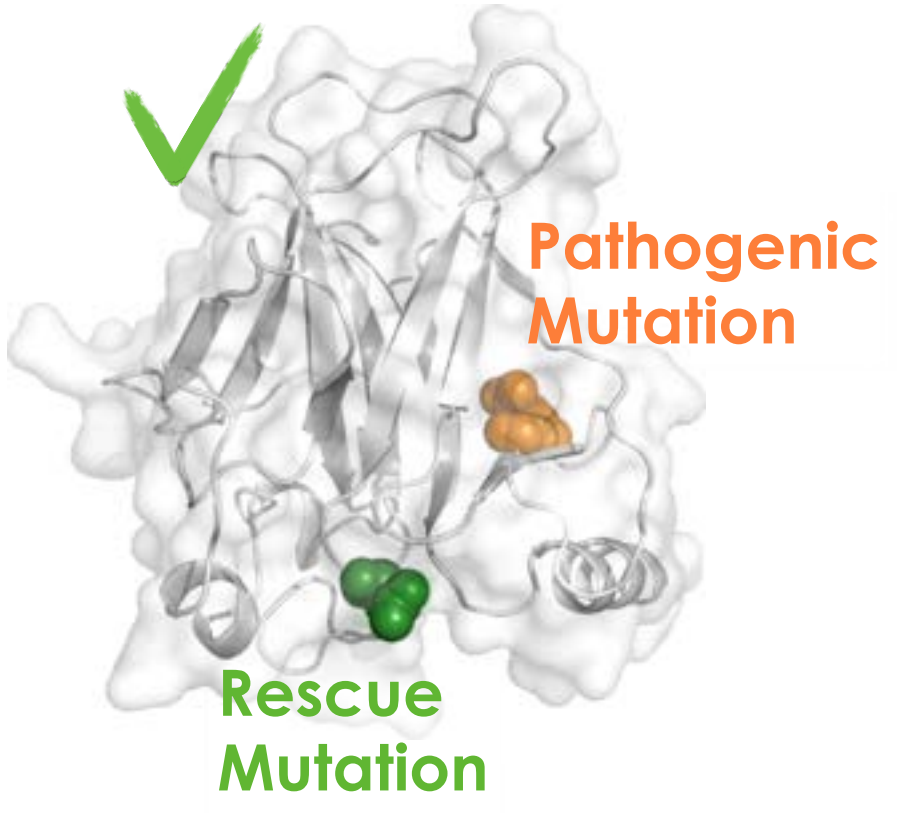
- OM has a double effect on myosin dynamics
- Interactions involved could be used for drug development
- OM to be tested for DCM mutation rescuing

S. Hashem, M.Tiberti, A. Fornili, (2017) PLoS Comput Biol13(11): e1005826.

Rescue mutants and drug design



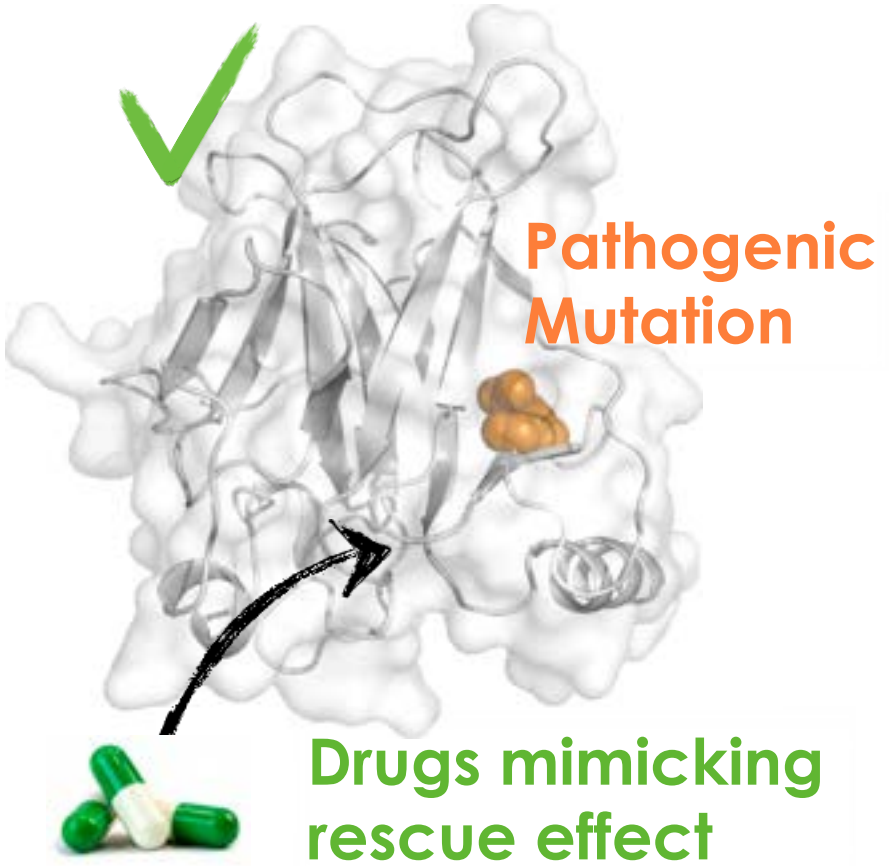
Rescue mutants and drug design



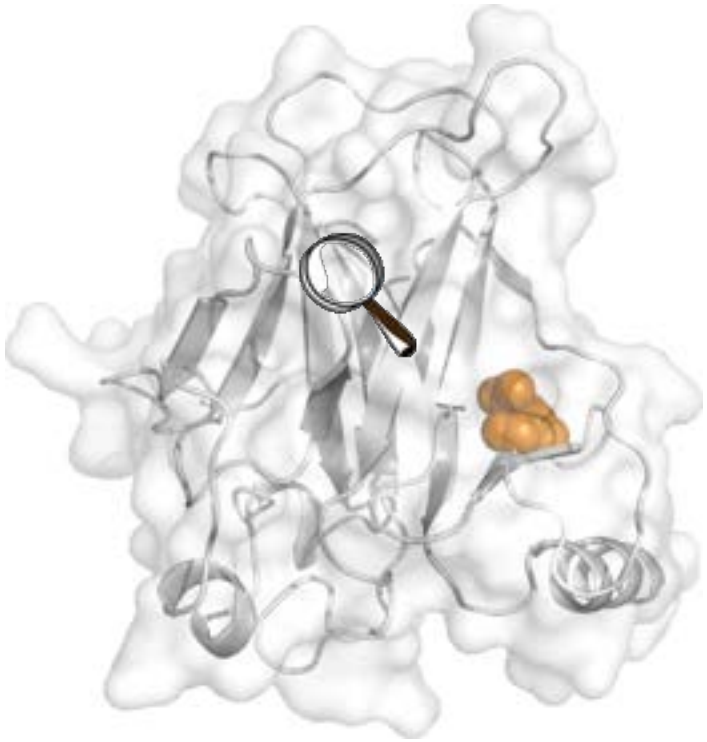
Protein function can be rescued by restoring:

- Structure
- Dynamics
- Thermodynamic stability
- Interactions with partners

Rescue mutants and drug design



Prediction of rescue mutants

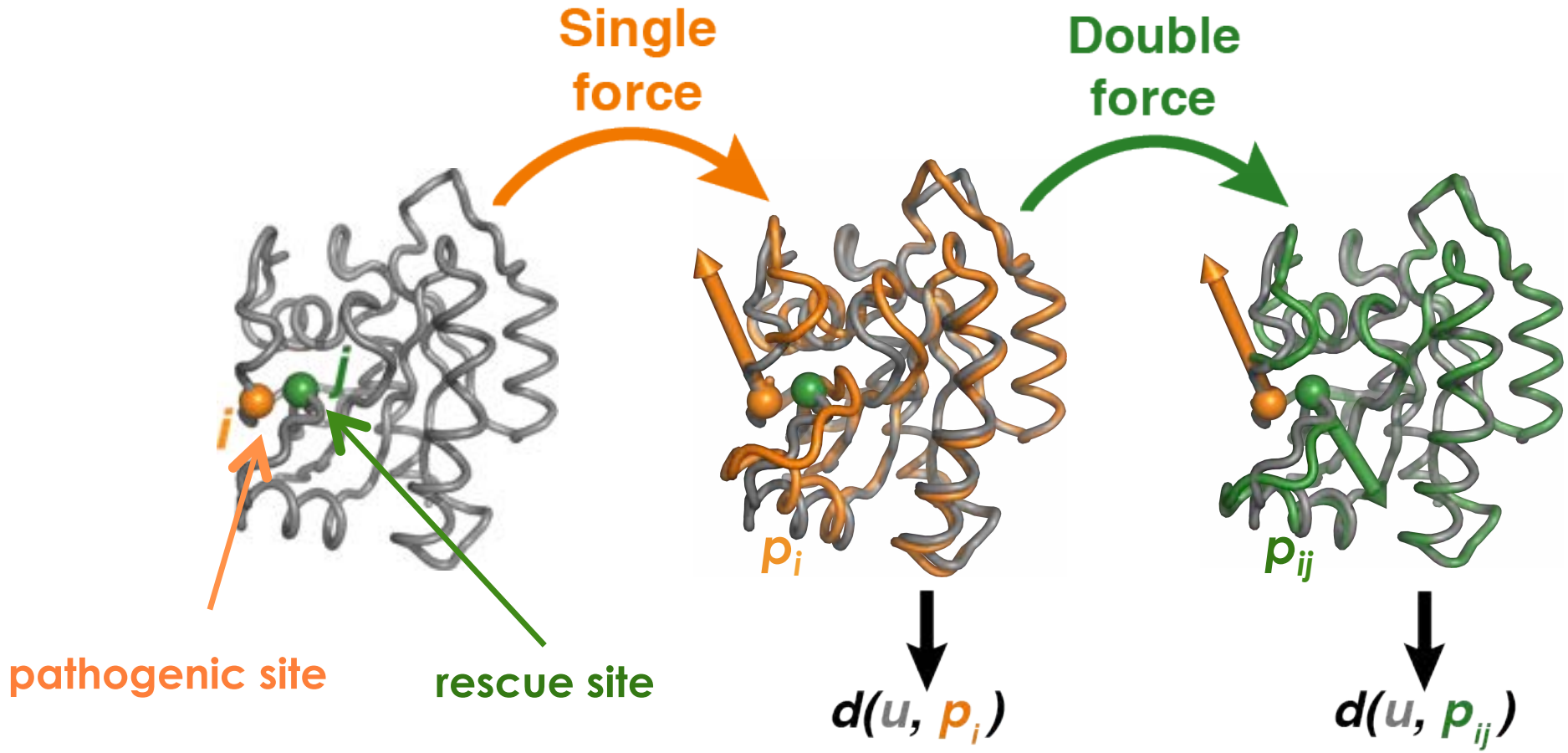


Double Force Scanning

https://fornililab.github.io/dfs/

M.Tiberti, A. Pandini, F. Fraternali, A. Fornili, Bioinformatics, 2017, doi: 10.1093/bioinformatics/btx515.

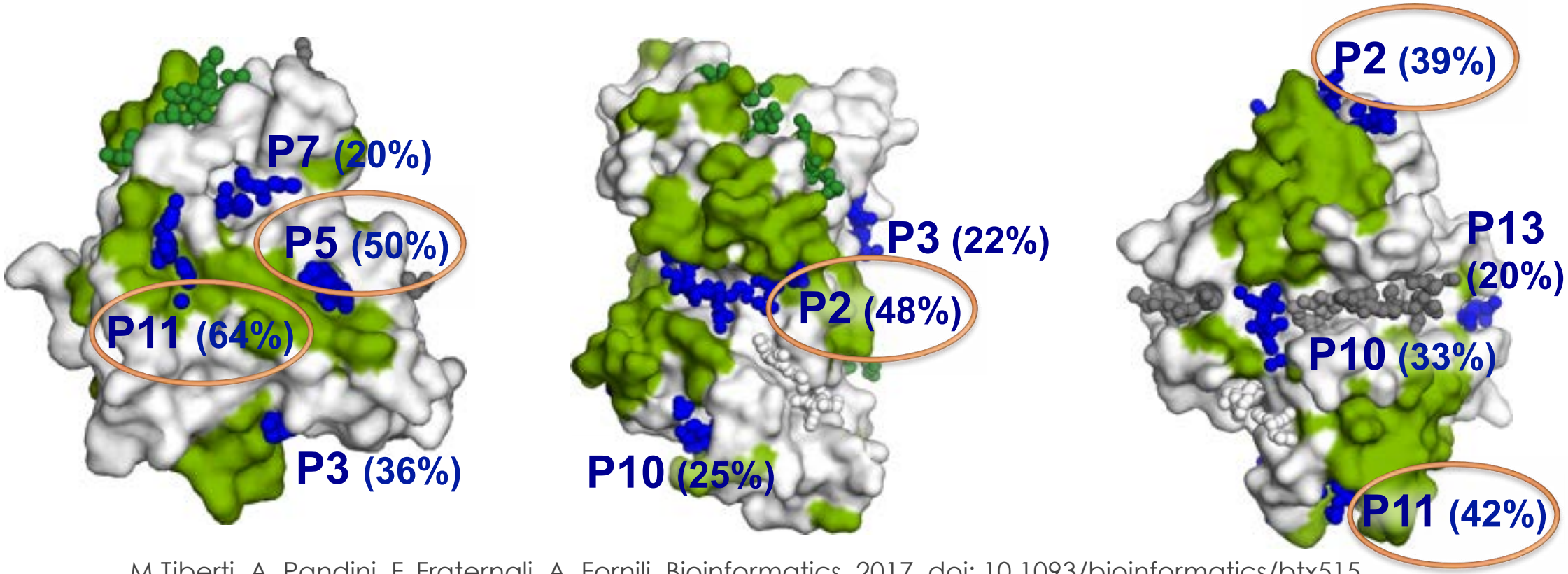
Prediction of rescue mutants



Compensatory effect when $d(u, p_{ij}) < d(u, p_i)$

Prediction of rescue mutants

Drug binding pocket prediction + DFS ➡ compensatory pockets



M.Tiberti, A. Pandini, F. Fraternali, A. Fornili, Bioinformatics, 2017, doi: 10.1093/bioinformatics/btx515.

Prediction of rescue mutants

- General
- Only 3D structure required
- Relatively fast (~hours for average size)

Double Force Scanning

https://fornililab.github.io/dfs/

M.Tiberti, A. Pandini, F. Fraternali, A. Fornili, Bioinformatics, 2017, doi: 10.1093/bioinformatics/btx515.

Acknowledgements

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Franca Fraternali

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British Heart Foundation

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