In silico studies of the mutant protein causing cystic fibrosis

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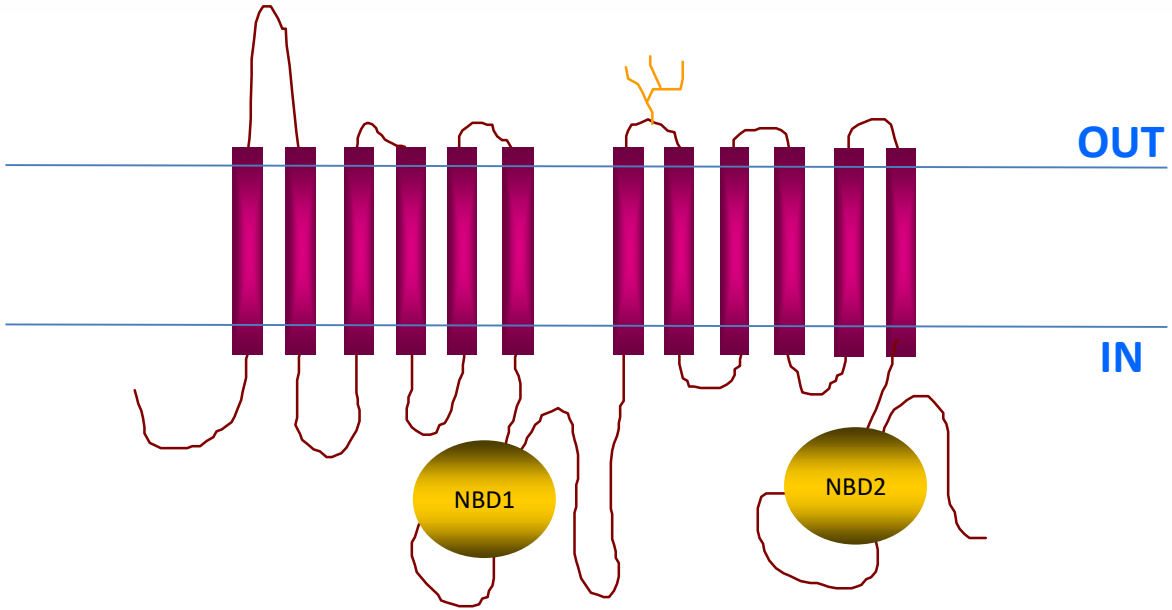
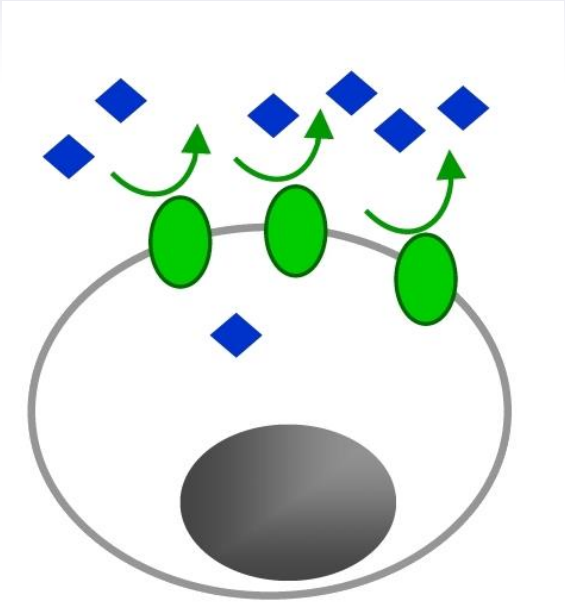
ABC (ATP Binding Cassette) transmembrane proteins



Transport of xenobiotics and toxic molecules



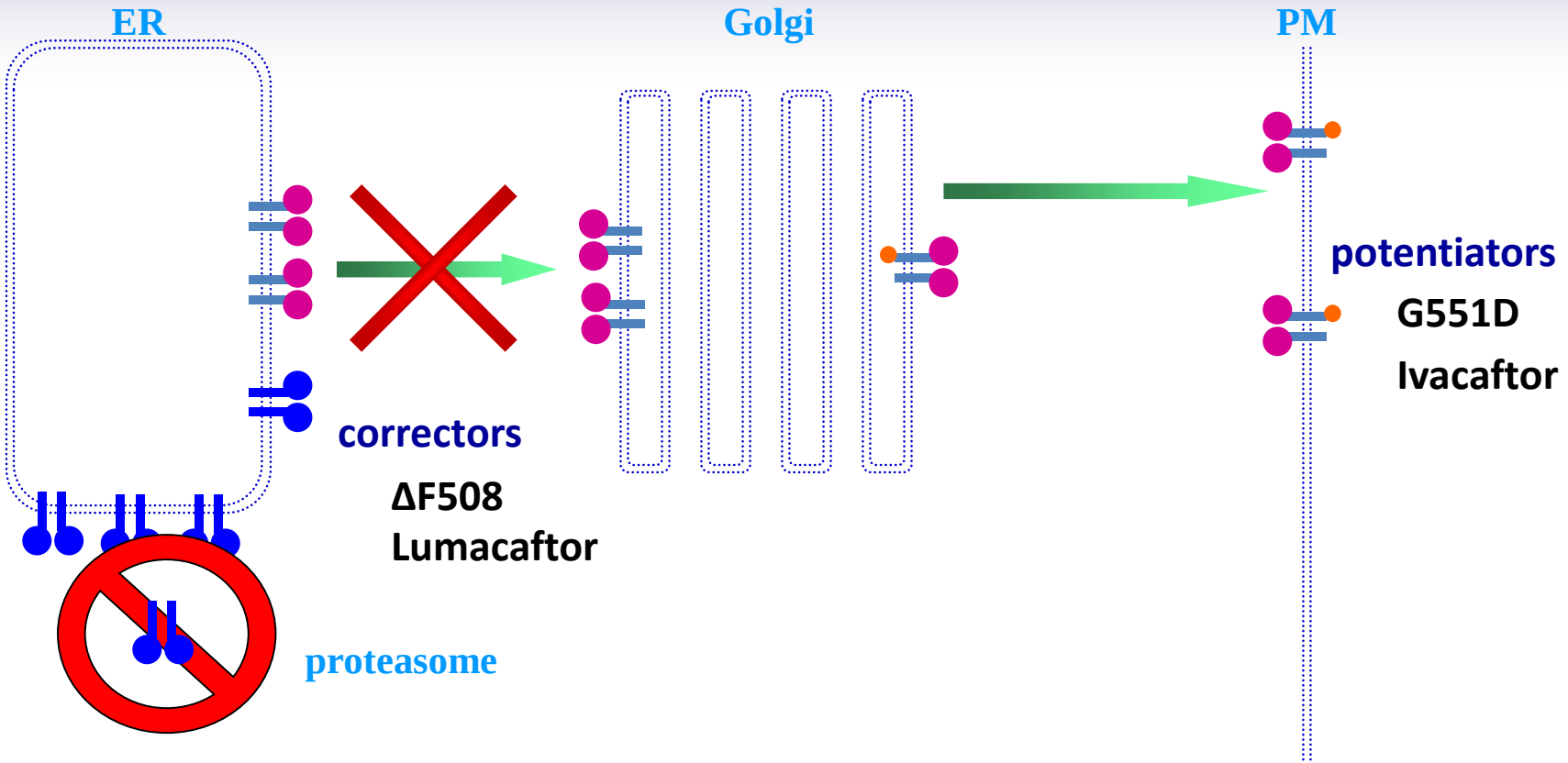
Keywords:

- cancer multidrug resistance
- drug pharmacokinetics
- drug-drug interactions, etc.

Cystic Fibrosis (CF)

- **monogenic disease** (~1:2,500)
- **high mortality and morbidity**
- **affected water and salt homeostasis**
- **cloning the *cftr* gene:** Riordan *et al.* 1989 *Science* **245**:1066-73
- **over 2,000 mutations are known**
- **ΔF508 is present in over 80% of patients**

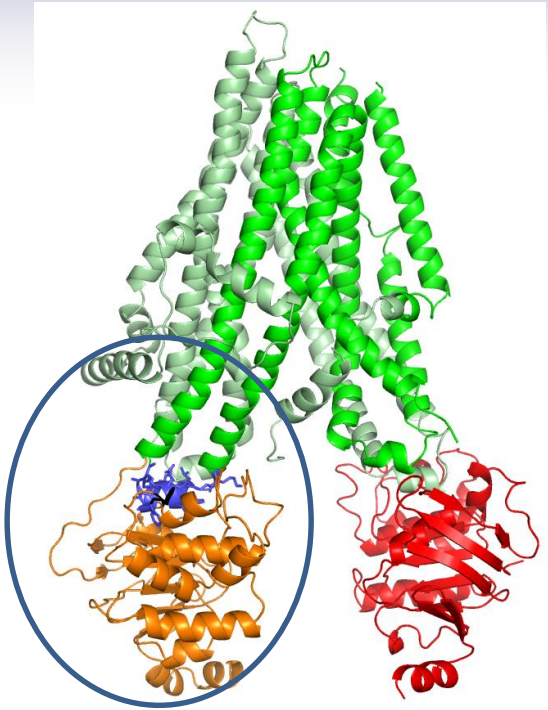
Maturation of the CFTR protein

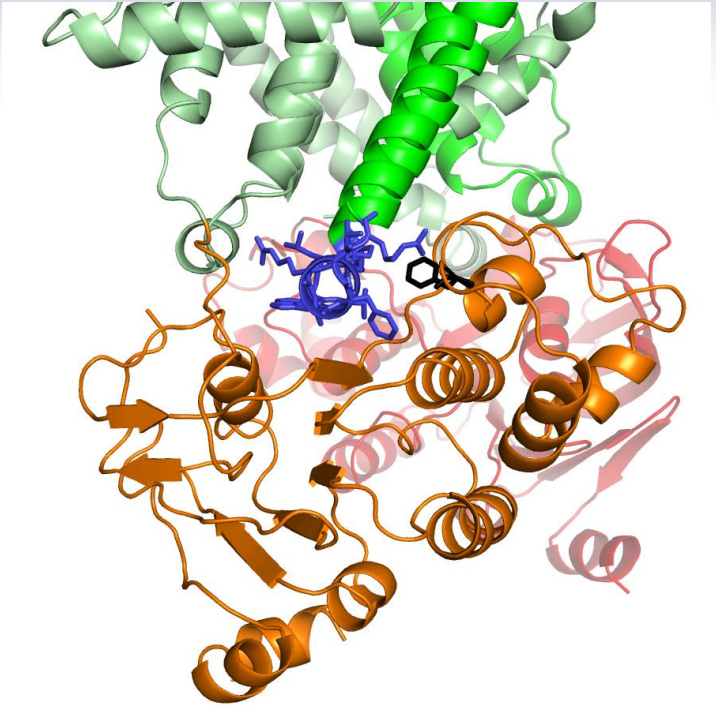


Structural background of ΔF508

domain-domain interactions

hCFTR (PDBID:5U71)





Du *et al.* Nat Struct Mol Biol. **2005** Jan;12(1):17-25.

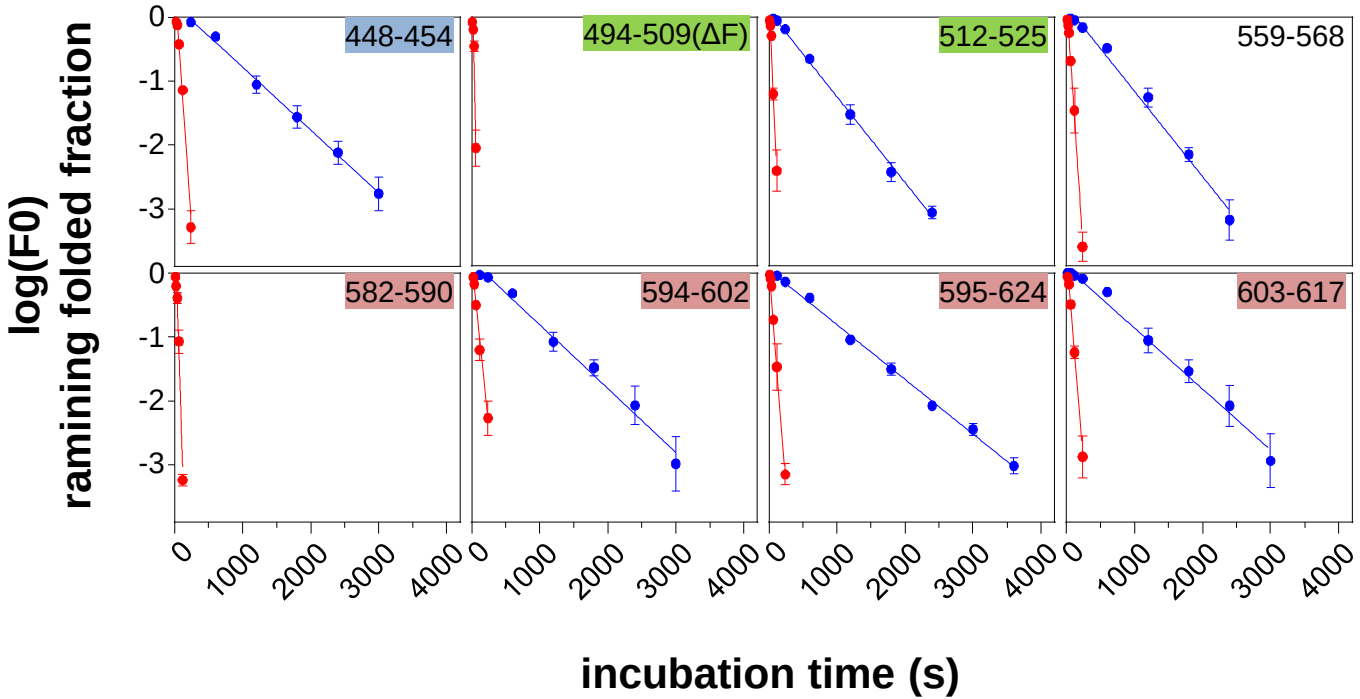
Serohijos *et al.* Proc Natl Acad Sci U S A. **2008** Mar 4;105(9):3256-61.

Structural background of ΔF508

folding and stability of NBD1

NBD1

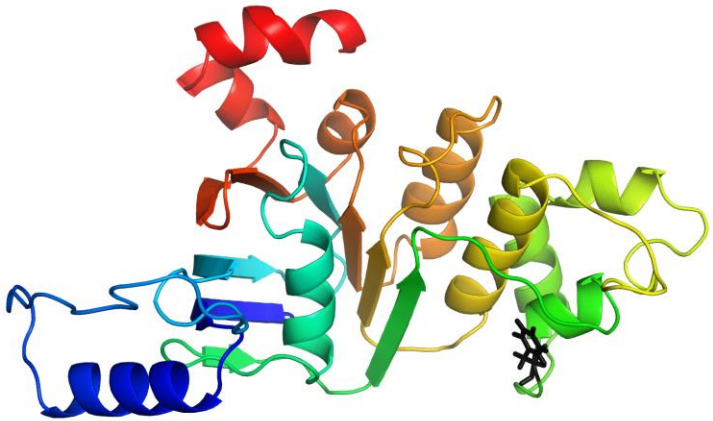
Experiment: Hydrogen-Deuterium Exchange (HDX)



In silico study of NBD1 destabilization

1. Molecular dynamics (MD) simulations
   - WT and mutants
   - 100-100 ns
   - *all-atom force field*

2. Analysis of motions in NBD1
   - correlations in motions (pairwise)
   - building a graph
   - analysis of the graph



Correlation in motions

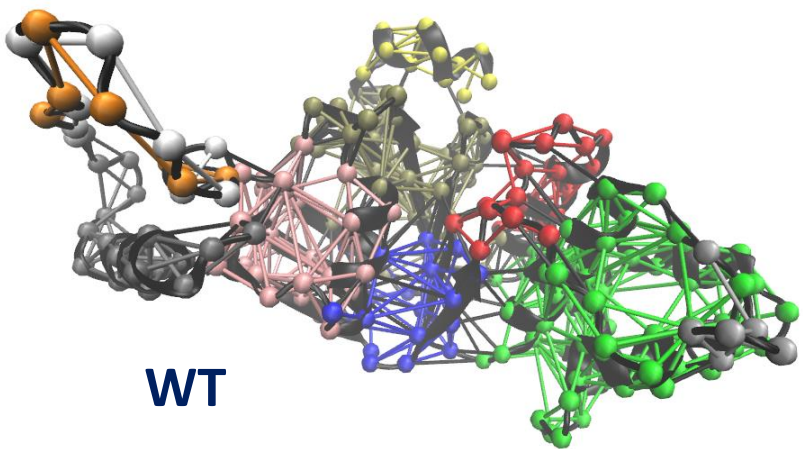
Nodes: amino acids

Edges:

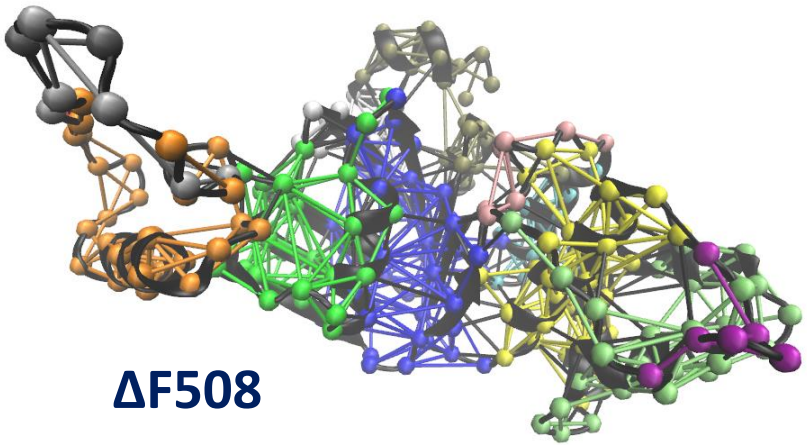
- **displacement Vector Correlation Coefficient**
- **Contact over 75% throughout the simulation**

$$\mathrm{VCC} = \frac{\langle (\mathbf{A} - \langle \mathbf{A} \rangle)(\mathbf{B} - \langle \mathbf{B} \rangle) \rangle}{\sqrt{\langle (\mathbf{A} - \langle \mathbf{A} \rangle)^2 \rangle \langle (\mathbf{B} - \langle \mathbf{B} \rangle)^2 \rangle}}$$

Community analysis (e.g. critical nodes)



WT



ΔF508

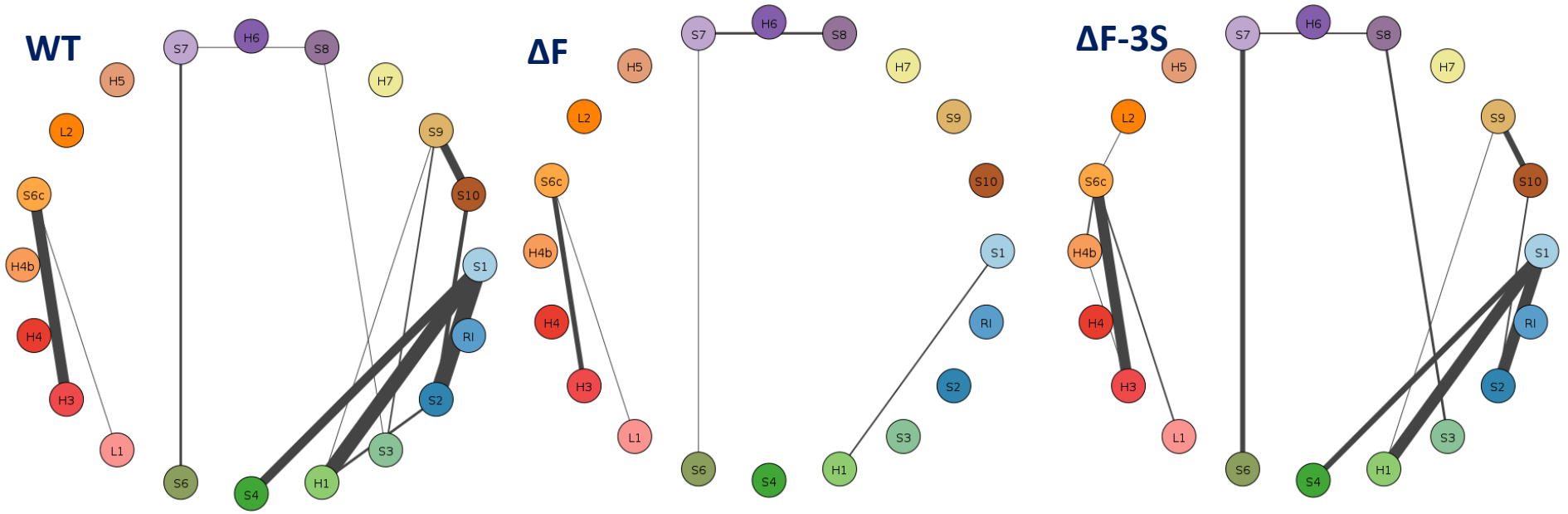
Distance Correlation Coefficient

G. J. Szekely *et al.* (2007), Annals of Statistics, 35 (6): 2769–2794.

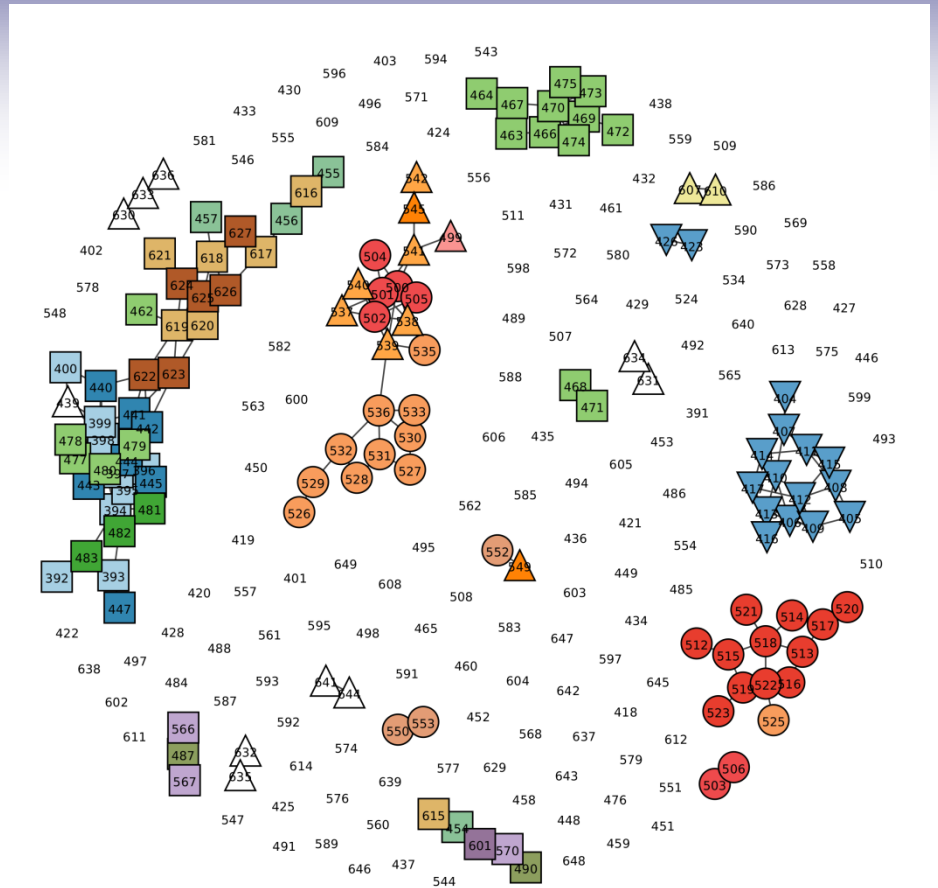
$$\mathrm{DiCC} = \frac{\nu(\mathbf{A}, \mathbf{B})}{\sqrt{\nu(\mathbf{A}, \mathbf{A})\nu(\mathbf{B}, \mathbf{B})}}$$

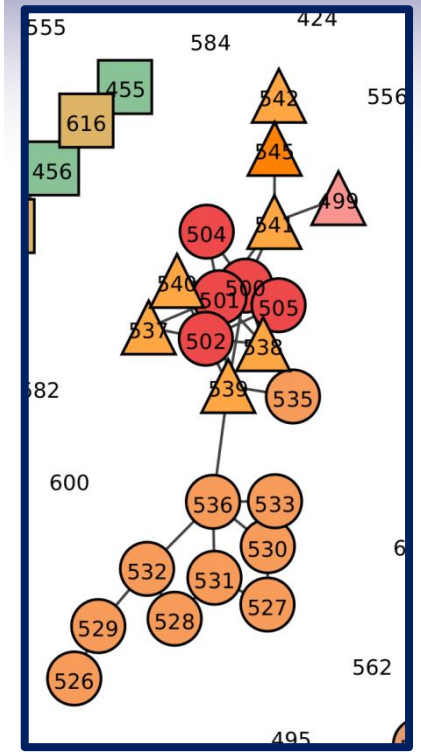
Nodes: secondary structural elements

Edges: if DiCC > 0.85



Identification of critical amino acids

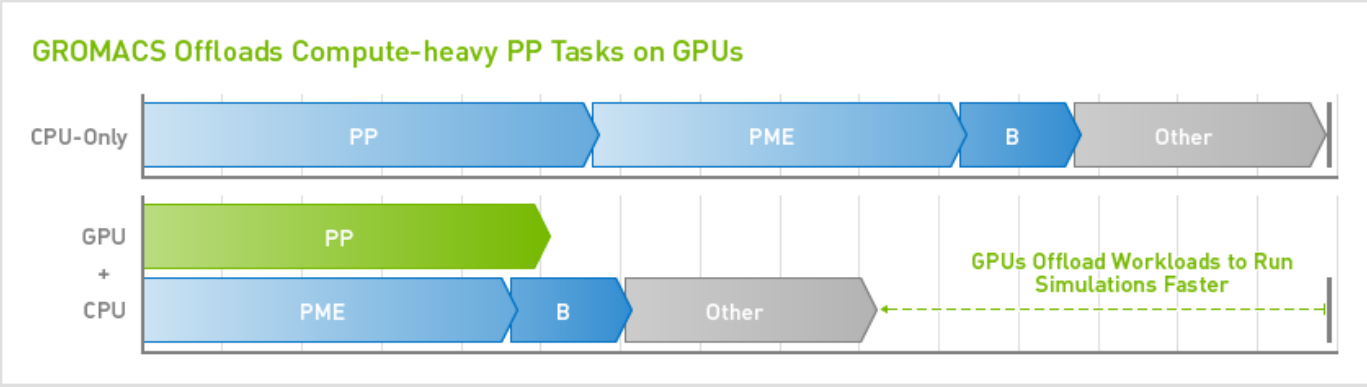




Utilization of GPUs #1

Running MD simulations, GROMACS

http://www.nvidia.com/object/running-jobs-in-gromacs.html



PP: Calculate short range non-bonded forces or particle-particle (PP) interactions

PME: Calculate an approximation for the long range part of long range non-bonded forces

- intensive internode communication
- 3DFFT

Moving PME to GPU worth only if job runs on a single node

Utilization of GPUs #2

Analyzing the trajectories, DiCC

$$\mathrm{DiCC} = \frac{\nu(\mathbf{A}, \mathbf{B})}{\sqrt{\nu(\mathbf{A}, \mathbf{A})\nu(\mathbf{B}, \mathbf{B})}}$$

$$\nu(\mathbf{A}, \mathbf{B}) = \sqrt{\frac{1}{n^2} \sum^{ij} \alpha_{ij}\beta_{ij}}$$

where

$$\alpha_{ij} = a_{ij} - a_{i.} - a_{.j} + a_{..} \qquad (2)$$

The following steps are needed to calculate α_{ij} from $\{\mathbf{A}\}$.

1. Build the $n \times n$ matrix, a, from $\{\mathbf{A}\}$, where a_{ij} is the distance between the ith and jth entries of $\{\mathbf{A}\}$: $a_{ij} = |\mathbf{A}^i - \mathbf{A}^j|$
2. Average the rows of $\mathbf{a}$: $a_{i.} = (1/n)\sum_j a_{ij}$
3. Average the columns of $\mathbf{a}$: $a_{.j} = (1/n)\sum_i a_{ij}$
4. Average all elements of $\mathbf{a}$: $a_{..} = (1/n^2)\sum_{ij} a_{ij}$
5. Build the $n \times n$ matrix $\boldsymbol{\alpha}$ from $\mathbf{a}$ where $\alpha_{ij} = a_{ij} - a_{i.} - a_{.j} + a_{..}$

My best case scenario:

250 amino acids
(250x250 symmetric matrix)
n(frames) = len(vector) = 8000

approx 120Gb RAM
approx 1 hour run on

- **Intel 8 cores**
- **AMD 32 cores**

Summary

- We employ *in silico* tools to dissect important changes in protein dynamics and identify critical residues for drug development.
- Accelerating running and analysis of simulations are critical.
- The most challenging steps are the interpretation and presentation of the results.

Thanks for your attention!

Cystic fibrosis