Biology as a Search Problem

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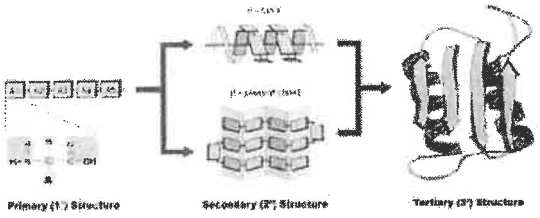
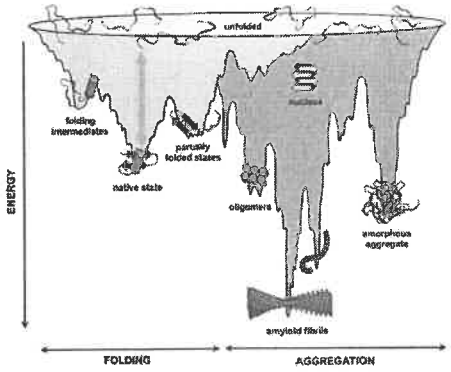
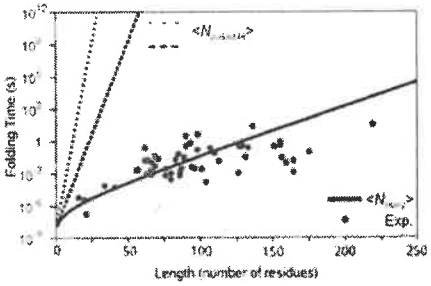
Preamble: Protein Folding



Many states in protein conformation space



How Do Proteins Fold So Quickly?



...but life chooses only a few

Lin & Zewail, *PNAS* 2012

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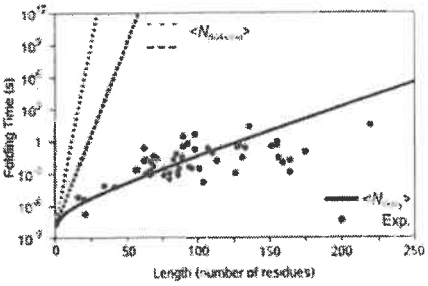
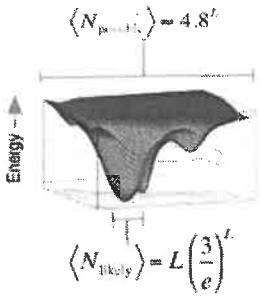
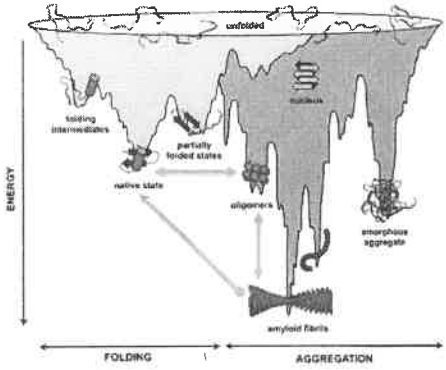




...there is a length limit

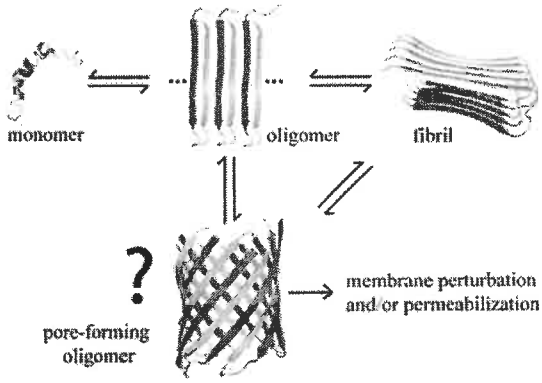
Lin & Zewail, *PNAS* 2012

Many states in protein conformation space



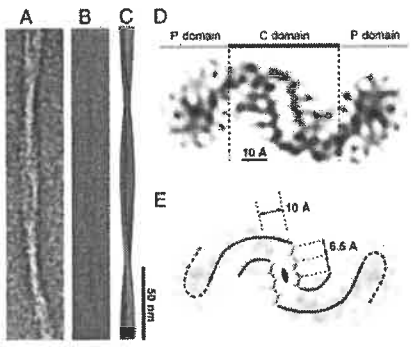
...but life chooses only a few

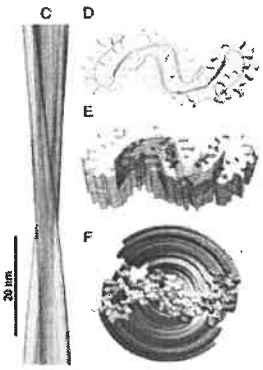
Unraveling how protein aggregation leads to Alzheimer's Disease



...and what kind of aggregate causes disease?

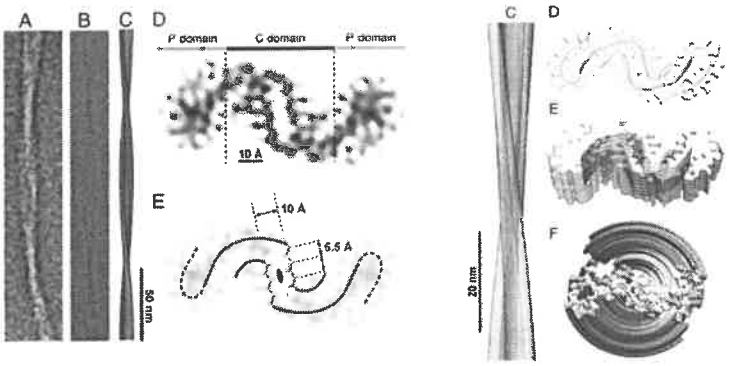
The amyloid is the easiest to see





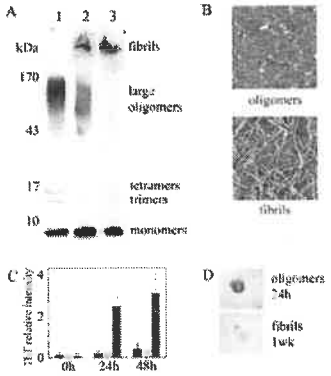
Schmidt et al, *PNAS* 2015

Much effort has focused on the amyloid



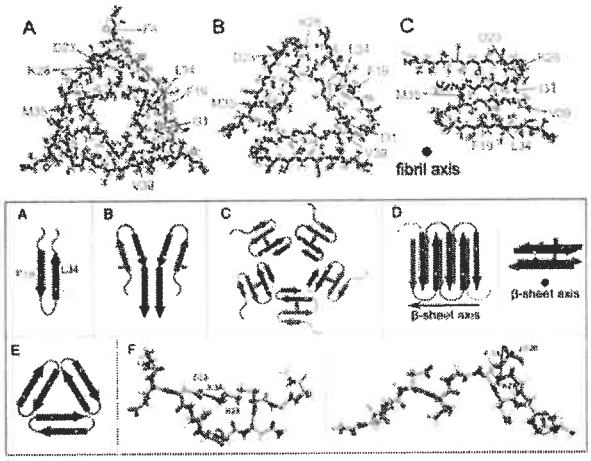
...yet drugs targeting the amyloid have all failed

In fact, the oligomers seem to be the toxic agents



perhaps we should find and target oligomer structure

There are many good guesses of the oligomer structure



Petkova, Leapman, Guo, Yau, Mattson, Tycko, *Science* 2005
Luhrs et al, *PNAS* 2005

Ahmed et al, *Nature Struc Mol Biol* 2010
Spencer, Li, Nowick, *J Am Chem Soc* 2014

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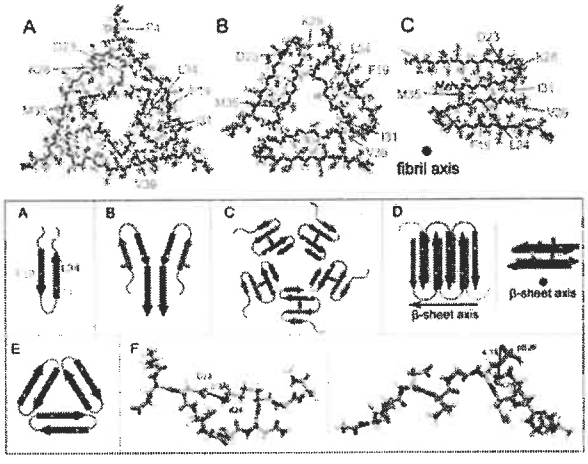
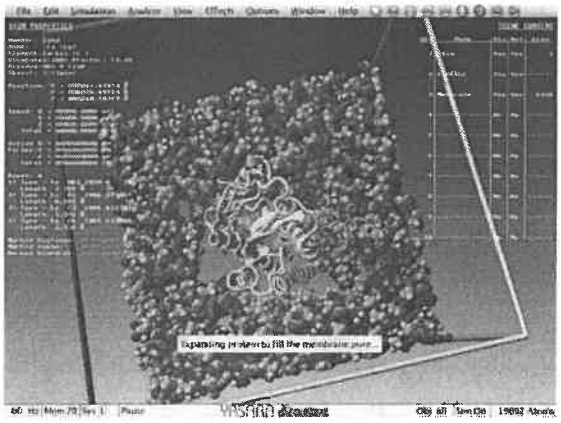
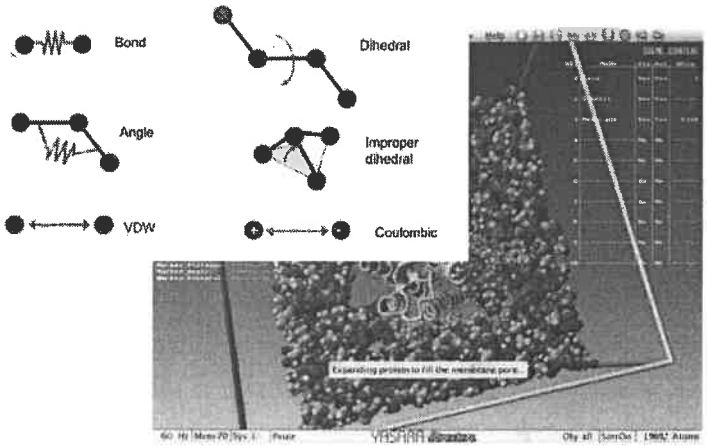


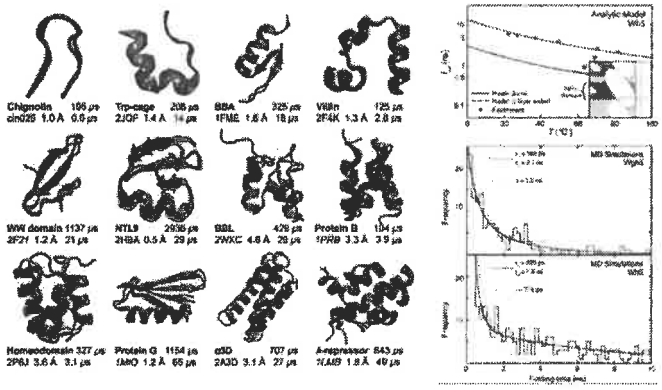
...but we do not yet know the structure(s)

Simulating protein folding using Newtonian mechanics





Simulating protein folding using Newtonian mechanics



Lindorff-Larsen et al, *Science* 2011

Lin et. al, *PNAS* 2011, 2012, 2014

This is hard to compute for two main reasons:

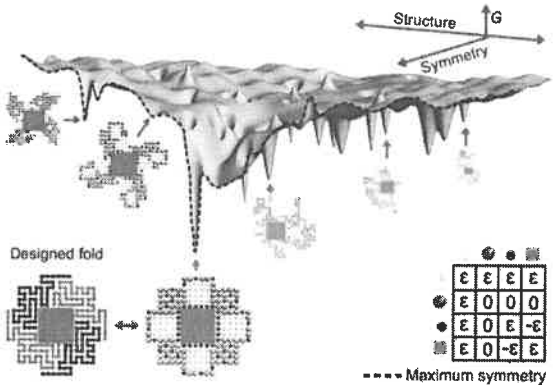
I. Conformational space is huge

conformation space scales as $e^{(L*N)}$
where *L*= protein length and N= # of proteins

II. Kinetic trapping

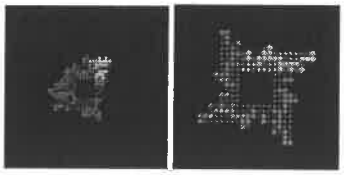
energy barriers of a few tens of kT are common for proteins

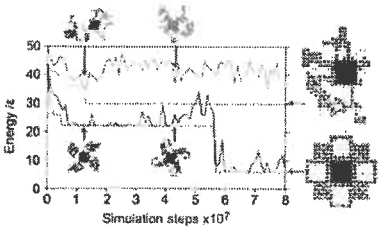
Tackling challenge I

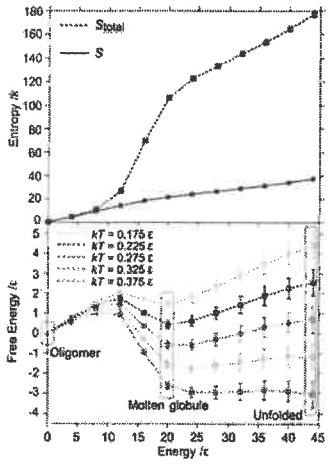


...there is folding symmetry that we can exploit

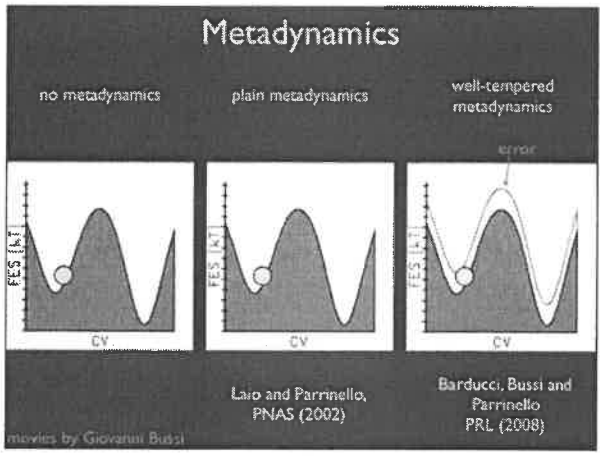
This works for a toy problem...



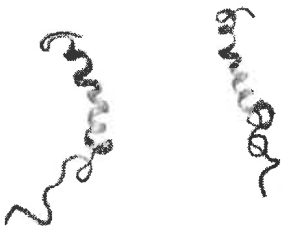




Tackling challenge II



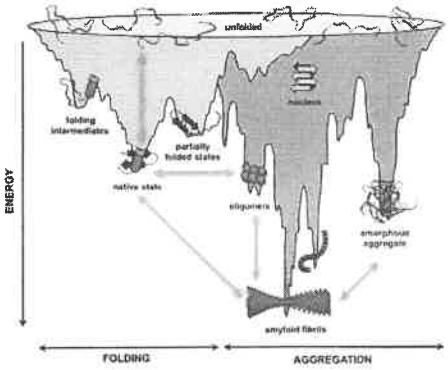
Abeta42 dimers



NO SYMMETRY CONSTRAINT

WITH SYMMETRY CONSTRAINT

A real free energy landscape for protein folding and aggregation



Thanks!

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