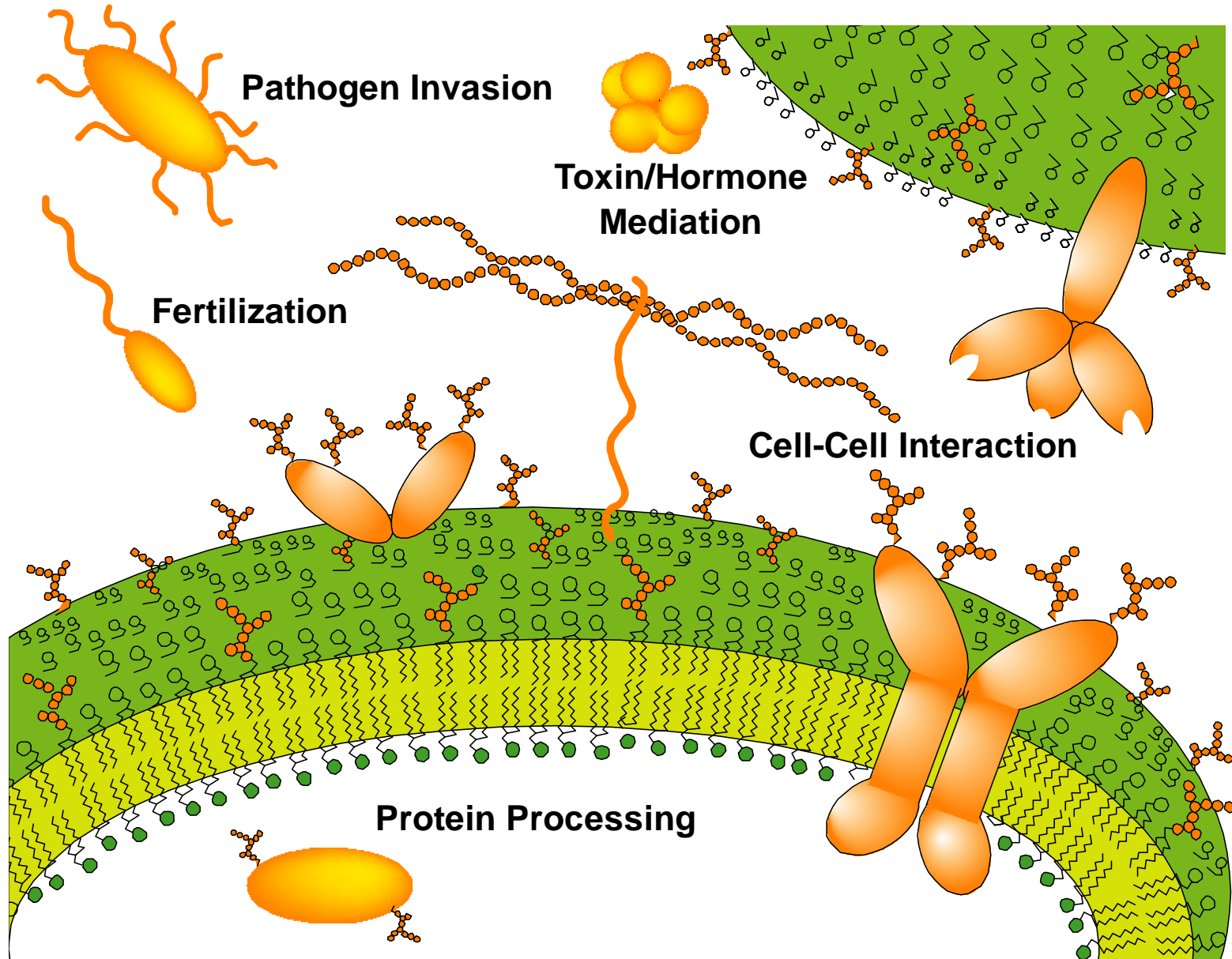


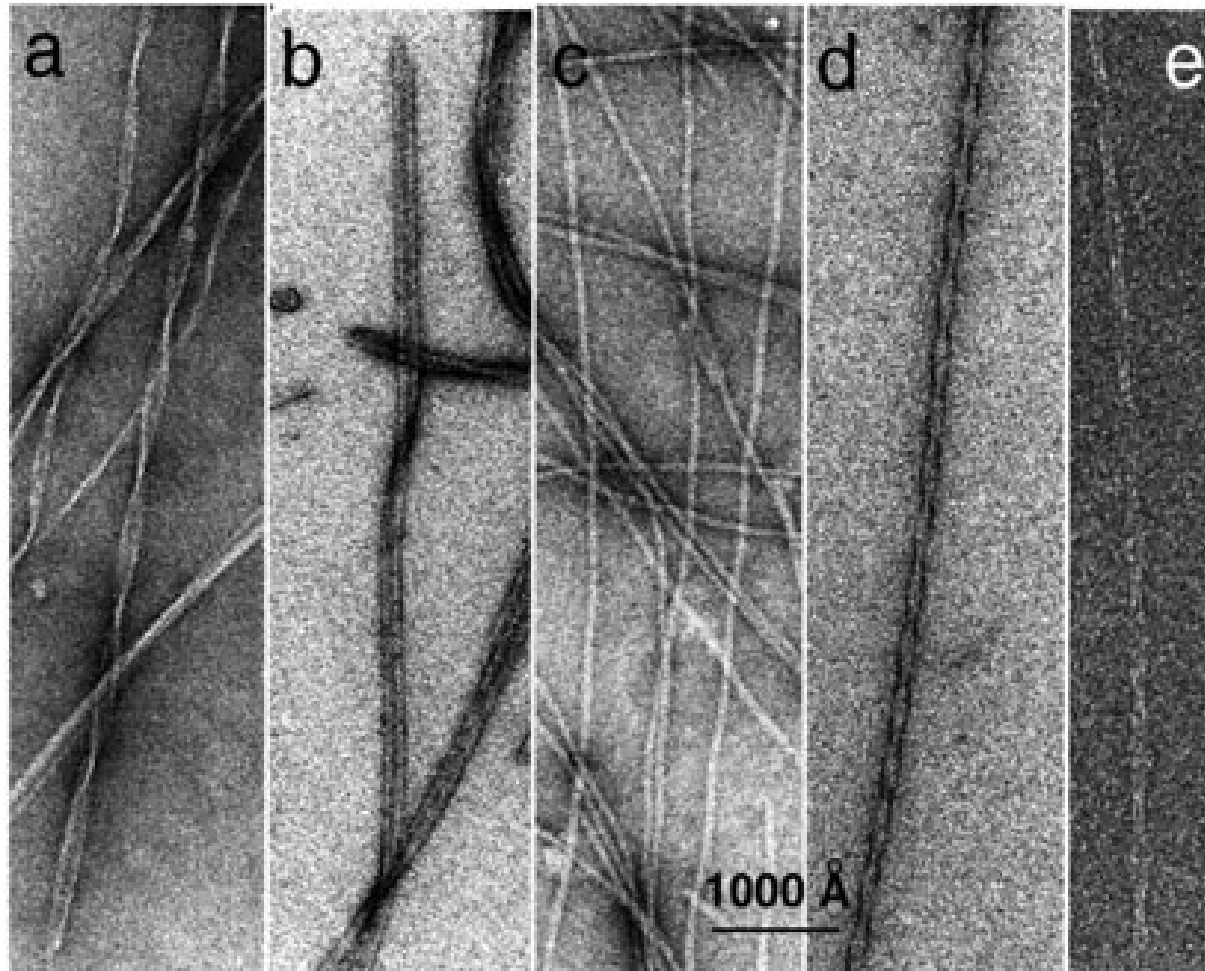
Interactions at Membrane Surfaces



Membrane Proteins

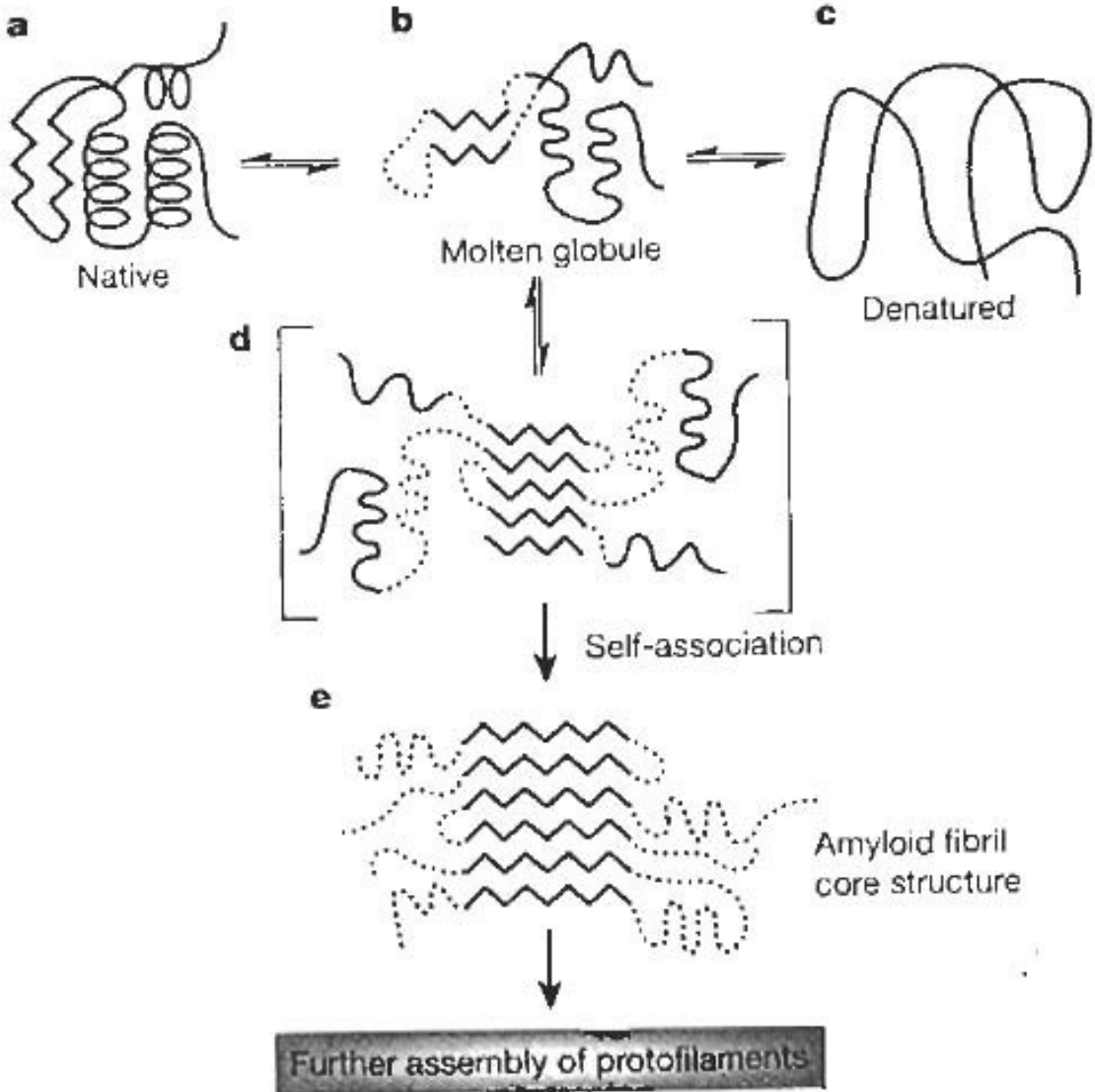
- About 30% of all genes appear to code for membrane proteins
- Only 3% of proteins deposited in the PDB are membrane proteins
- These proteins control a lot of biochemistry – oxidative phosphorylation
- Half of all drugs target G-protein coupled receptors
- Disease states such as Alzheimer's result from improper (?) processing of membrane proteins

42-46 Residue Peptides Cleaved from APP form Fibrils that assemble into Plaques

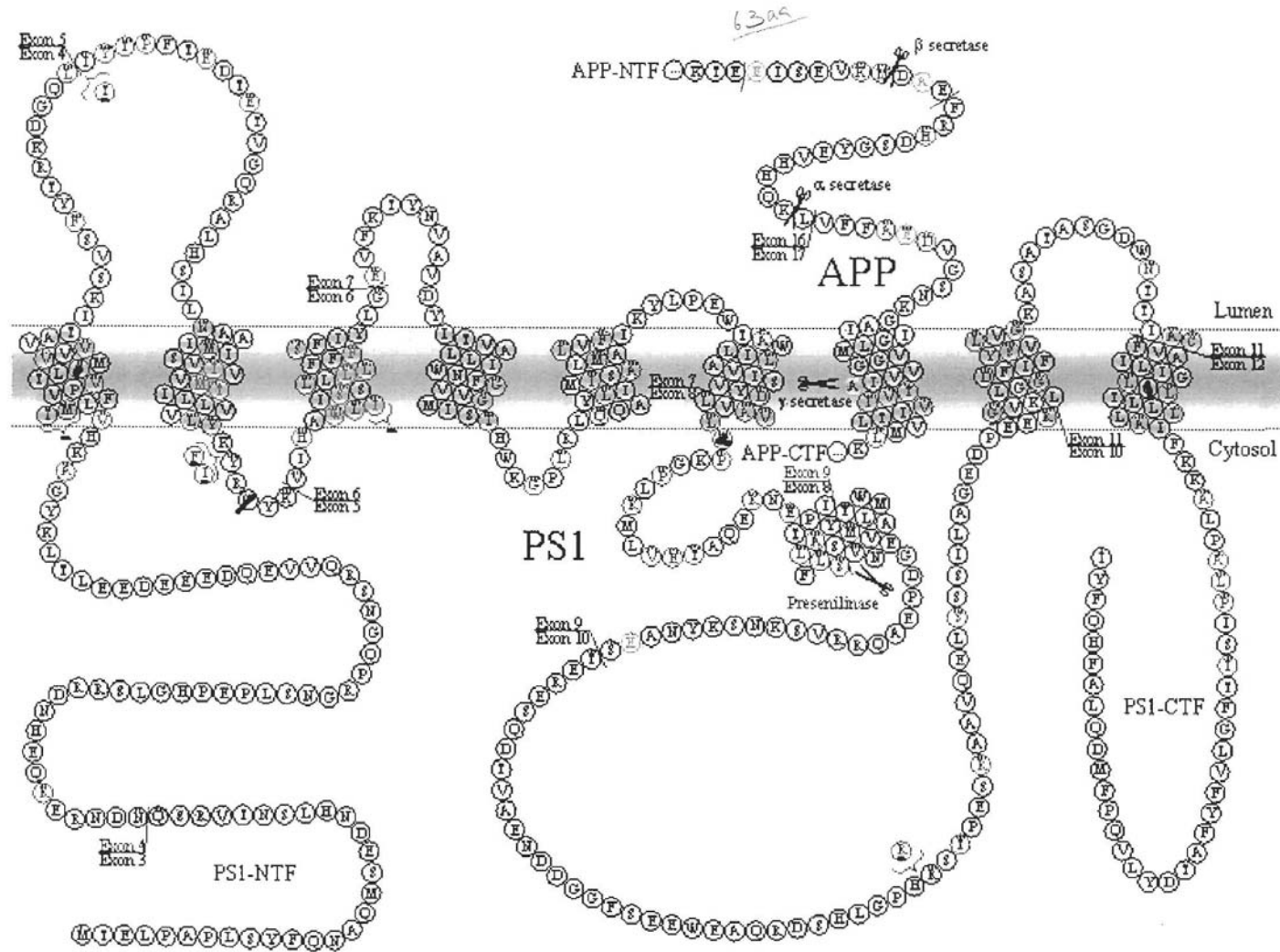


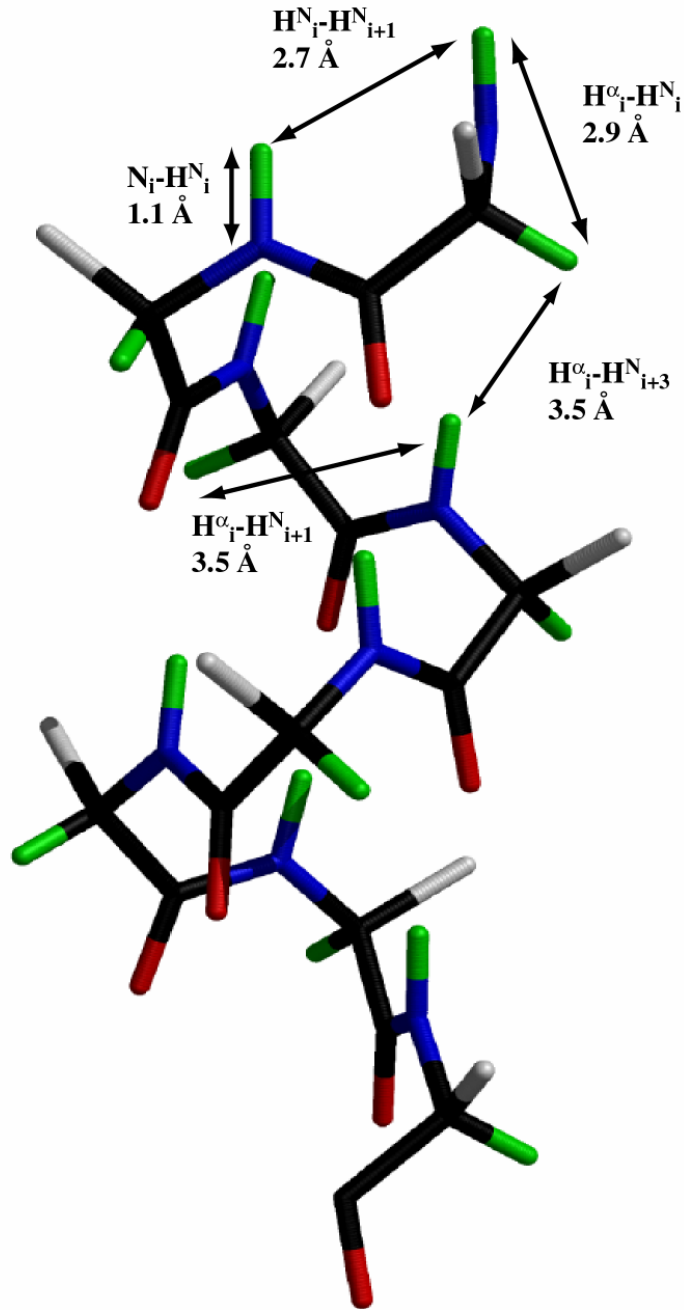
Cryo-EM images of fibrils from SH3 domain *The EMBO Journal* (1999)
18, 815–821, doi: 10.1093/emboj/18.4.815 José L. Jiménez et al.

Mechanism of Fibril Formation



Gamma Secretase is one Protein Responsible for processing Amyloid Precursor Protein





How do we identify membrane proteins from a sequence?

Alpha helix structures are common trans-membrane elements. Hydrogen bonds are satisfied, non-polar side-chains point out toward lipids

Predict Transmembrane Topology (MEMSAT2)

<http://bioinf.cs.ucl.ac.uk/psipred/>

Jones DT, Taylor WR, Thornton JM. (1994) A Model Recognition Approach to the Prediction of All-Helical Membrane Protein Structure and Topology. *Biochem.* 33: 3038-3049.

MEMSAT2 is the latest version of the widely used all-helical membrane protein prediction method MEMSAT. The method was benchmarked on a test set of 86 transmembrane proteins of known topology. From sequence data MEMSAT2 was able to accurately predict the topology of 80 out of the 86 test proteins. This gives MEMSAT2 an estimated accuracy of over 92% at predicting the structure of all-helical transmembrane proteins and the location of their constituent helical elements within a membrane.

Information Used in MEMSTAT Topology Predictions

- Helices are made of apolar residues
- Helices are of length 17-25 residues
- Helices are sometimes amphipathic
- Positive residues tend to be on inside loops
- Residues are classified as Li(inside loop), Lo(outside loop), Hi inside helix end, Hm(middle), Ho(outside helix end)
- Database of known membrane proteins is used to give statistical scores for each amino acid in each of these positions.

Results from MEMSTAT2 Analysis

```
10    20    30    40    50    60
-----OOOOXXXXXXXXXXXXXIIII+++++++IIIIXXXXXXXXXXXXXXXXXXXXXOOOO-----
MGA AVFFGCTFVAFGPAFALFLITVAGDPLRVILVAGAFFWLVSLLLASVVWFILVHVT

70    80    90    100   110   120
-----OOOOXXXXXXXXXXXXXIIII+++++++IIII+++++++IIII+++++++IIII
DRSDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISIRQMAYV

130   140   150   160   170   180
XXXXXXXXXXXXXXXXXXXXXOOOO-----OOOOXXXXXXXXXXXXXXXXXXXXXIIII+
SGLSFGIISGVFSVINILADALGPGVVGIIHG DSPYYFLTSAFLTAIILLHTFWGVVFFD

190   200   210   220   230   240
+++++++IIIIXXXXXXXXXXXXXOOOO-----OOOOXXXXXXXXXXXXXXXXXXXXXIIII+++++
ACERRRYWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLWAFITAGGSLRSI
Q

250   260
+++++++
RSLLCRRQEDSRVMVYSALRIPPEDDD
```

--- Key:
+ : Inside loop
- : Outside loop
O : Outside helix cap
X : Central transmembrane helix segment
I : Inside helix cap