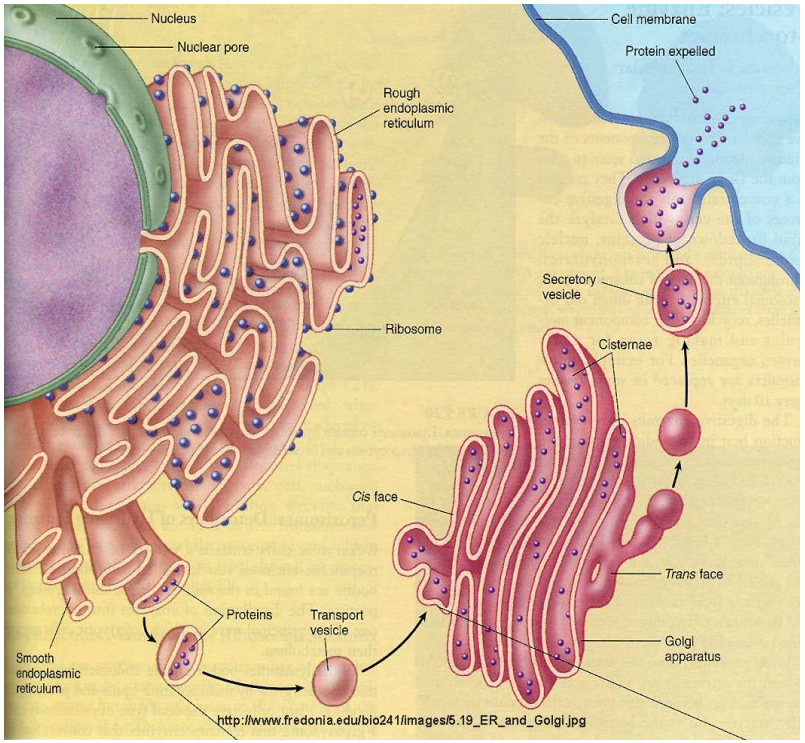
How is protein load sense in the endoplasmic reticulum?

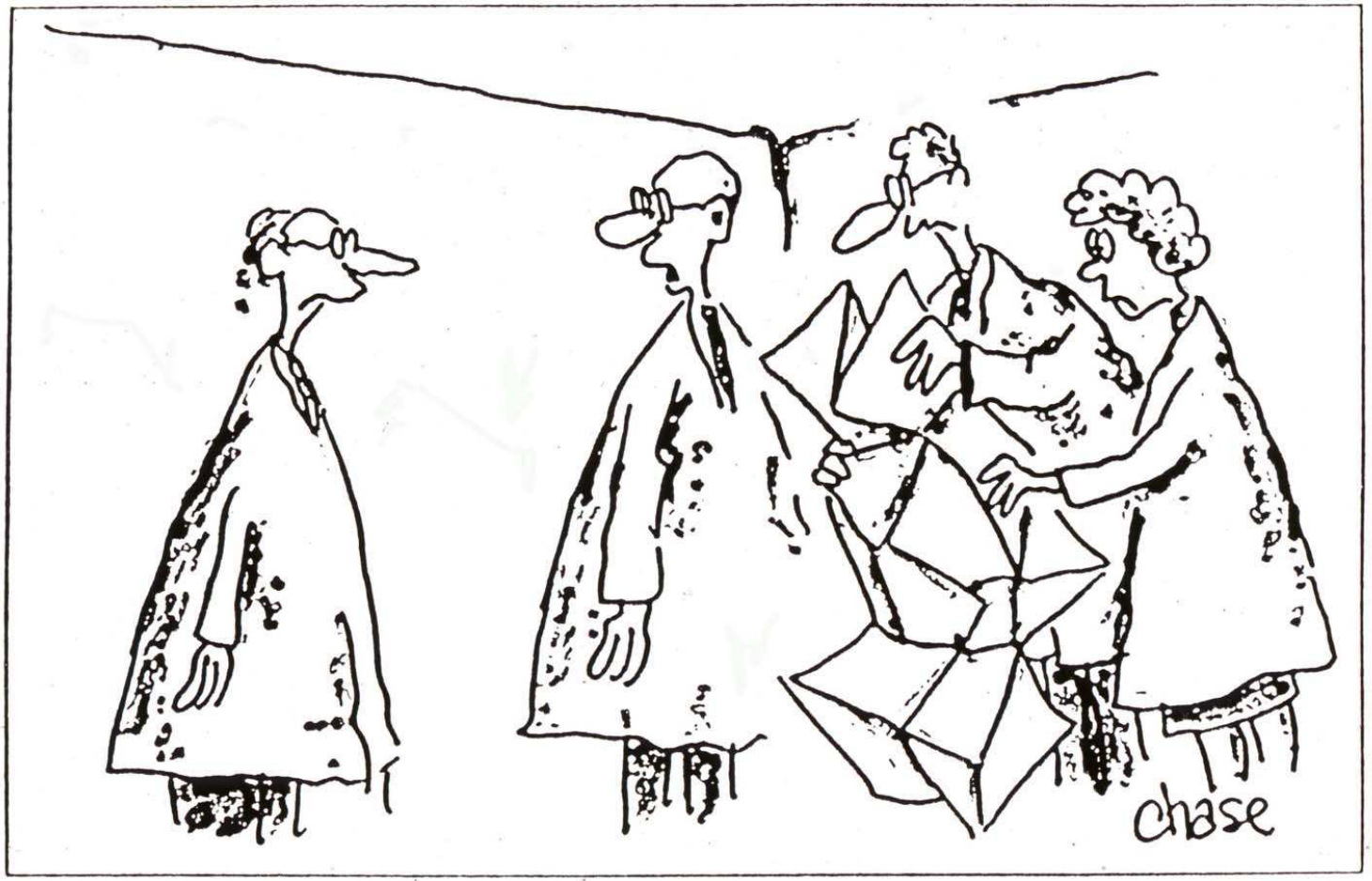
Miguel Rodriguez †
and Santiago Schnell † ‡ ¶
University of Michigan Medical School
† Department of Molecular and Integrative Physiology
‡ Center for Computational Medicine and Biology
¶ Brehm Center for Type 1 Diabetes Research and Analysis

E-mail: schnells@umich.edu
Web: sitemaker.umich.edu/schnell.lab



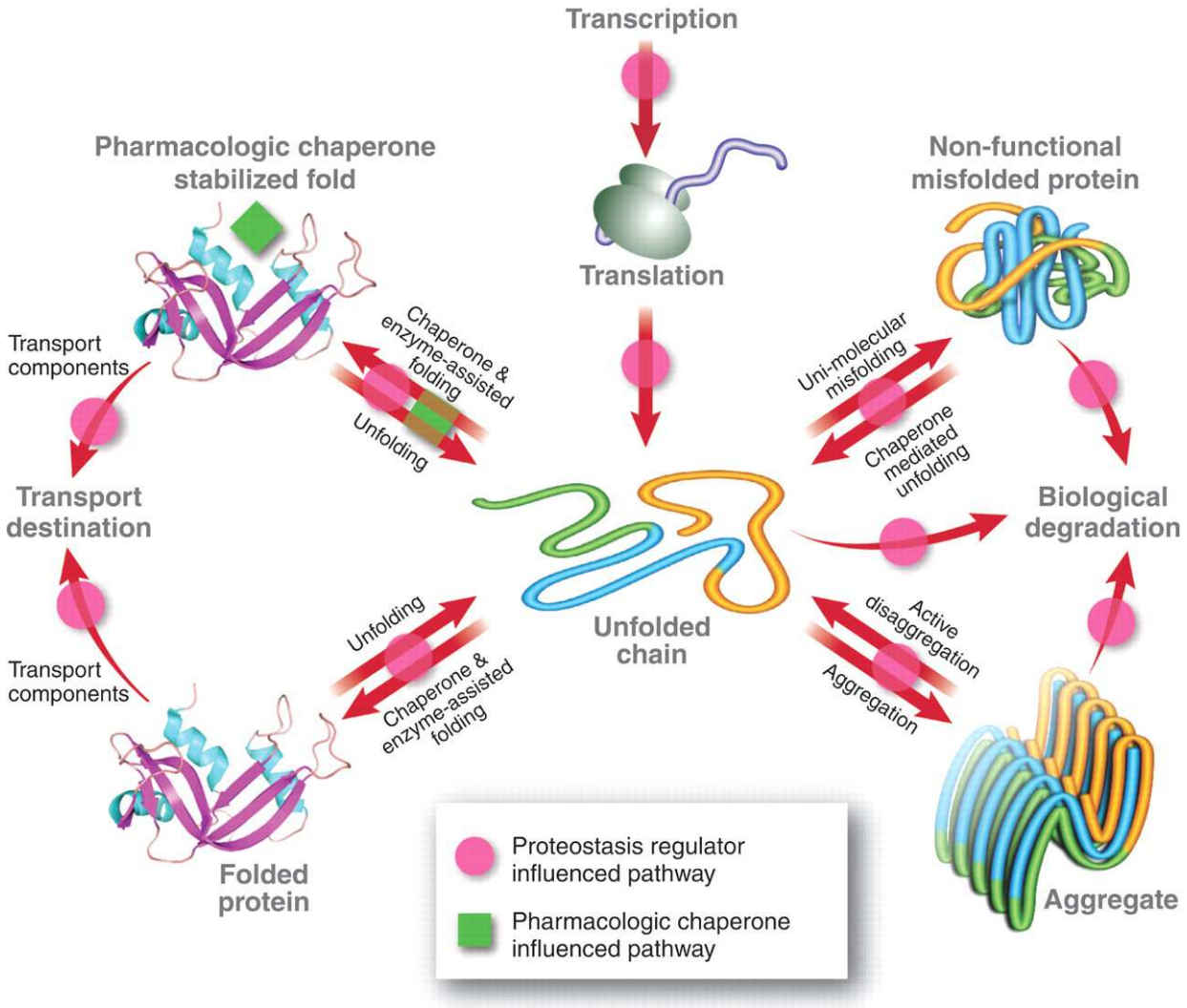
This work has been sponsored by Brehm Center for Type 1 Diabetes Research and Analysis

University of Michigan Health System



"We finished the genome map, now we can't figure out how to fold it!"

Protein folding is regulated through a complex "proteostasis" network

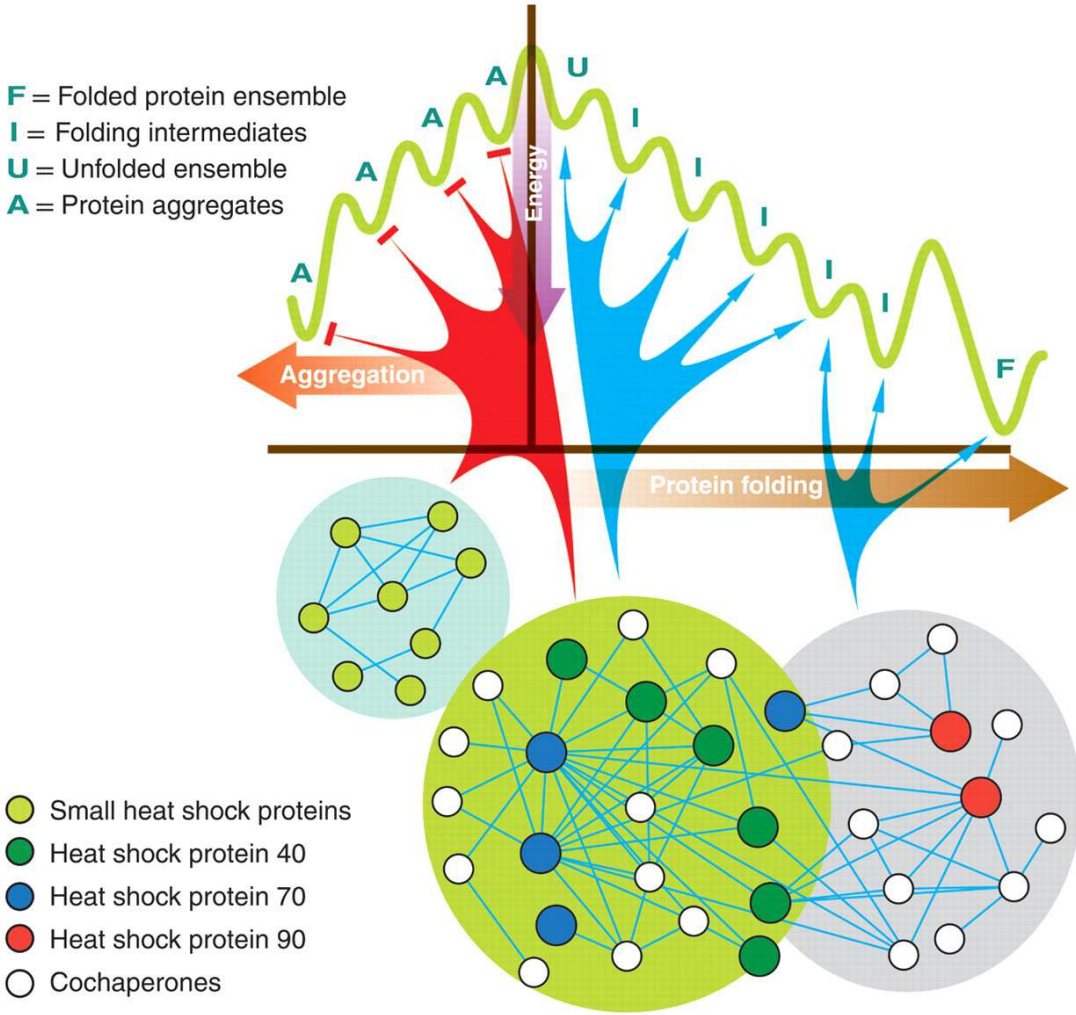


Balch et al. *Science* 2008; **319**:916-919

Failure in proteostasis is the cause of many diseases

Insulin	ER	Young Adult onset diabetes
Huntingtin	Nucleus and cytosol	Huntington
α-amyloid/presenilin	ER	Alzheimer's
p53	Cytosol	Cancer
Crystalins	Cytosol	Cataracts
Prion protein	ER	Creutzfeldt-Jakob
Fribillin	ER	Marfan syndrome
Cystic firbosis transmembrane regulator	ER	Cystic fibrosis
Collagen	ER	Osteogenesis imperfecta

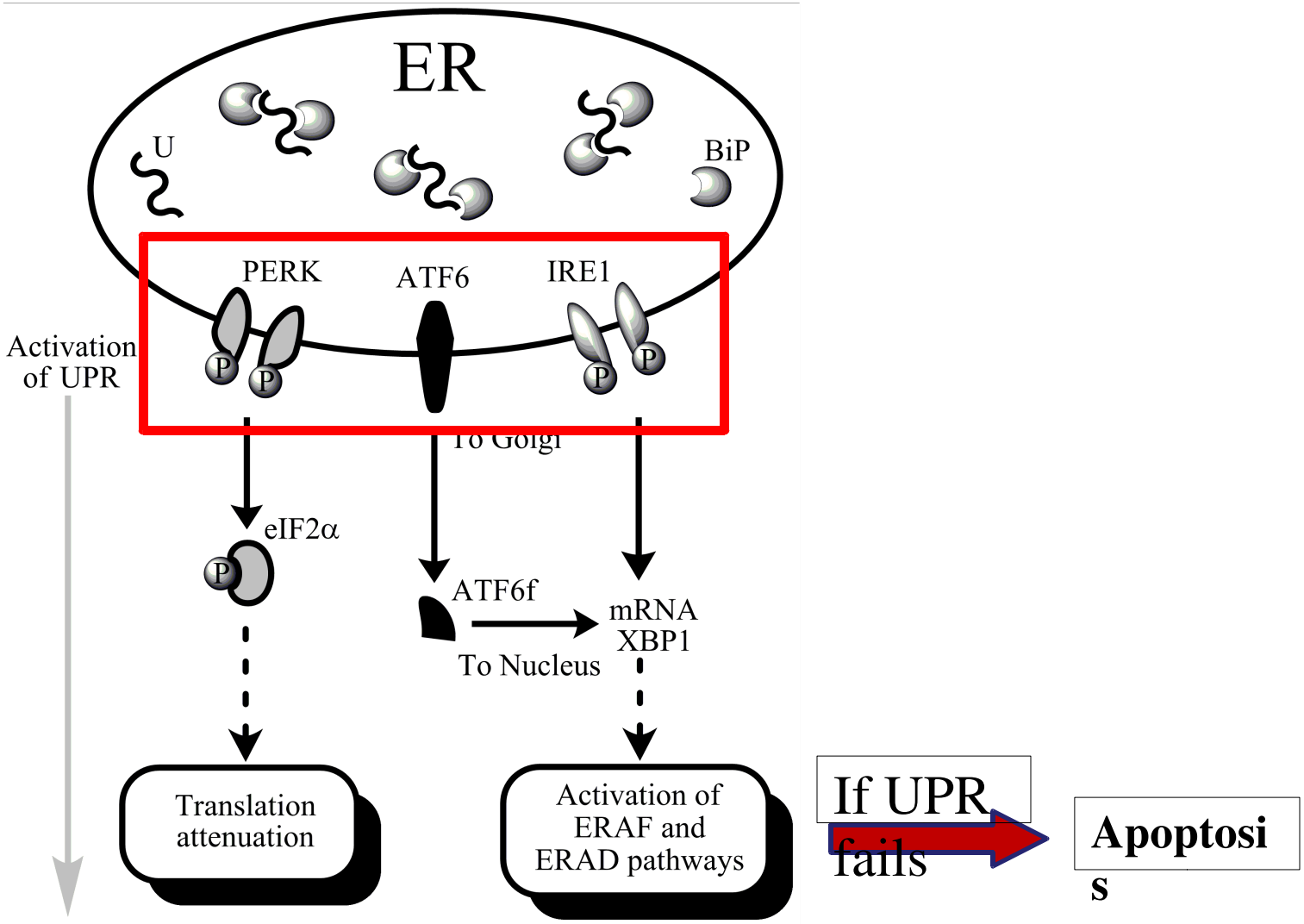
Protein folding diseases are prevented through chaperone/co-chaperone-assisted network



This signalling pathways is part of the unfolded protein response (UPR)

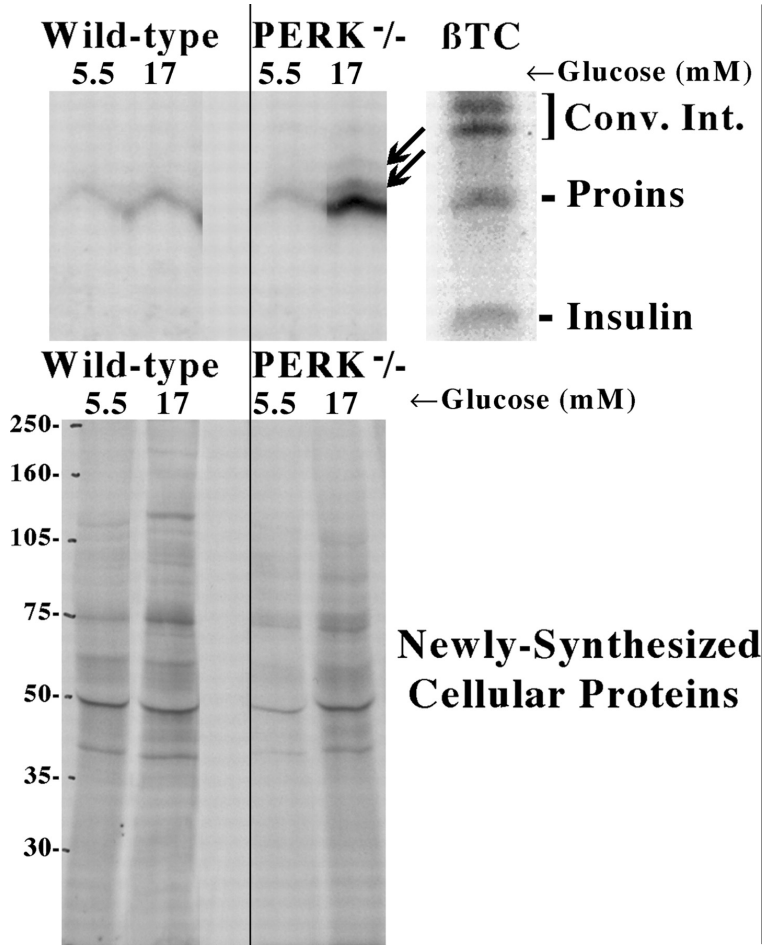
Balch et al. *Science* 2008; **319**:916-919

The unfolded protein response is activated by three ER stress transducers



Schnell *Cell Phys. Biochem.* 2009; **23**:233-244.

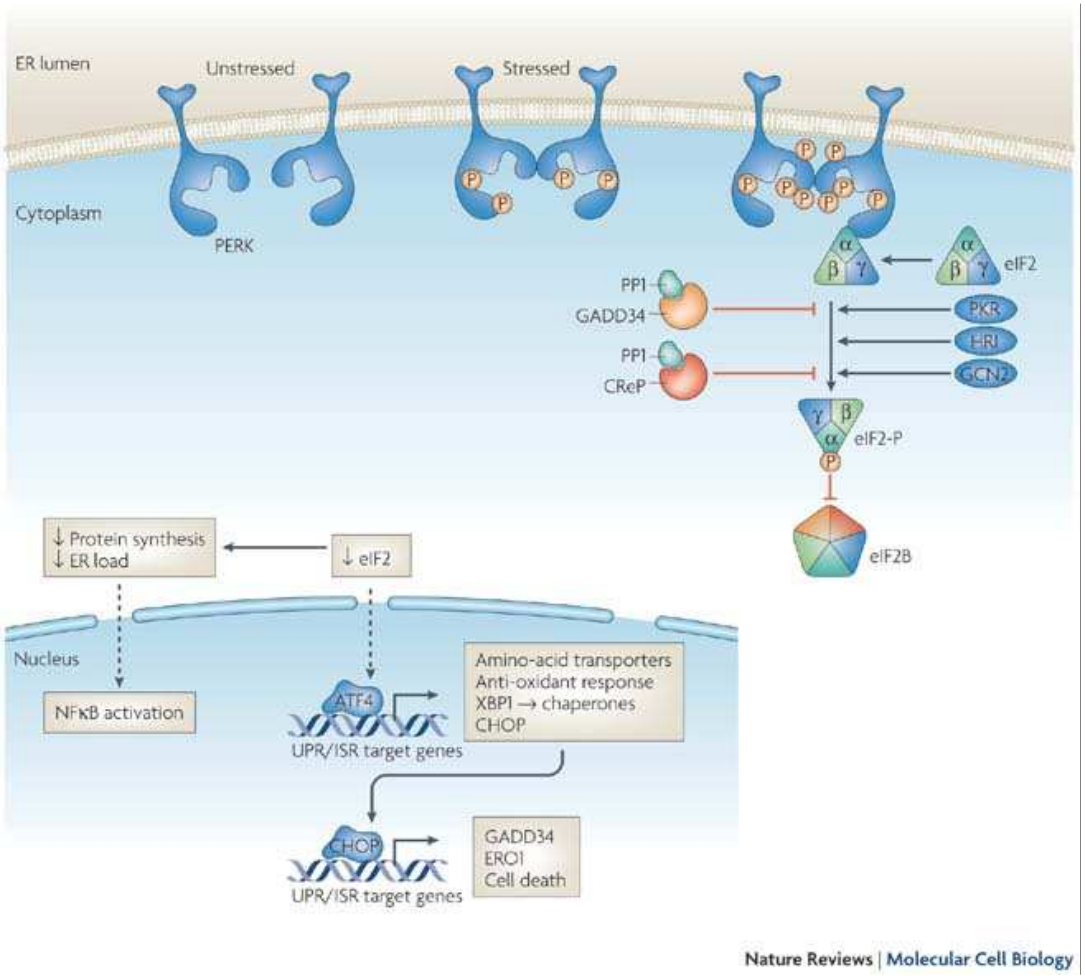
Proinsulin isomers increase their concentration in mice deficient for PERK



Liu et al. *J. Biol. Chem.* 2005; **280**:13209-13212

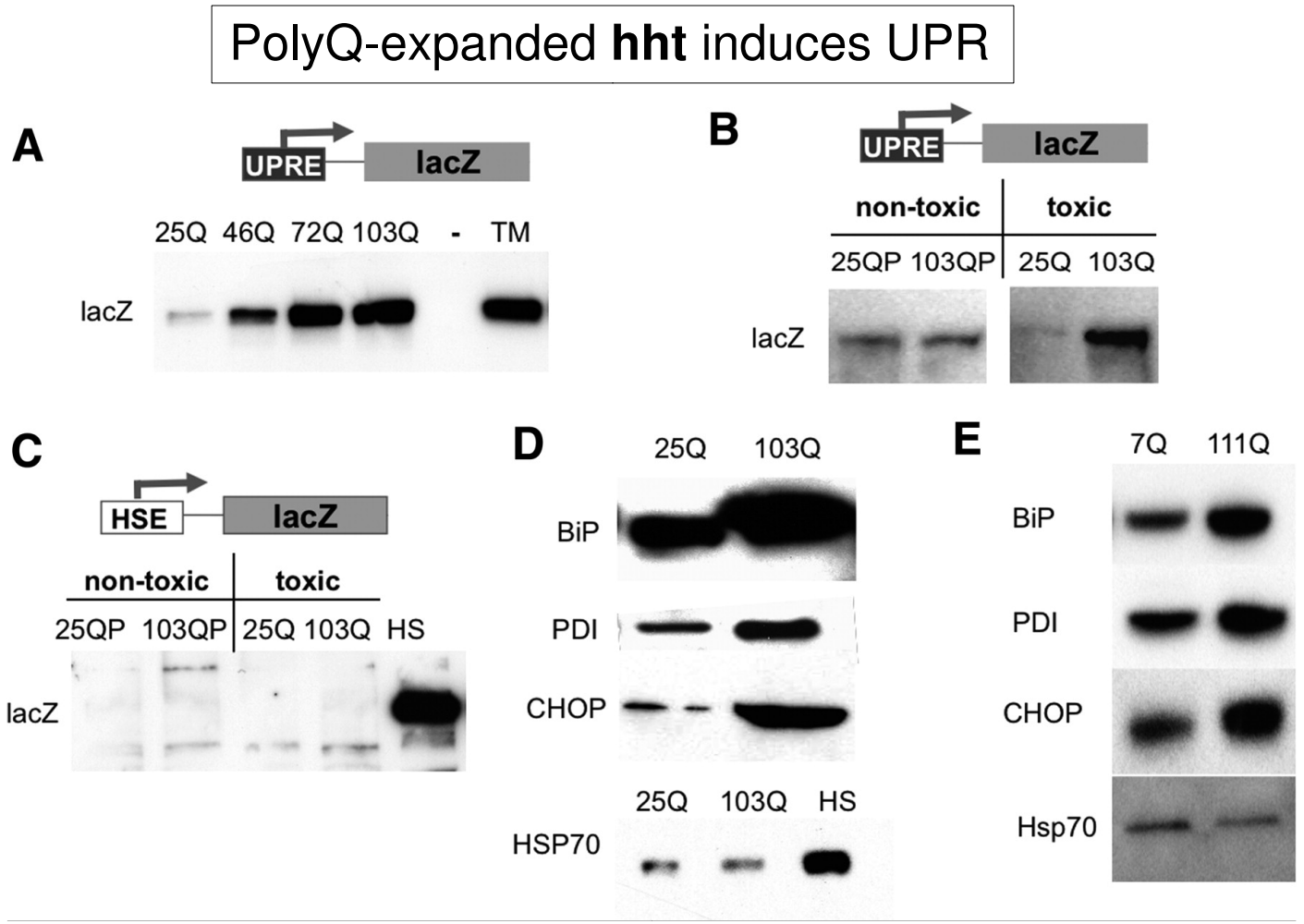
PERK signalling attenuates (or inhibits) translation of new proteins

Click to



Ron and Walter *Mol Cell Biol.* 2007; **8**:519-529.

UPR activation is characterized by immediate and drastic effect in the expression of ER-associate pathway components



Duennwald and Lindquist . *Genes Dev.* 2008;**22**:3308-3319

How is protein load sensed?

a. Direct recognition model

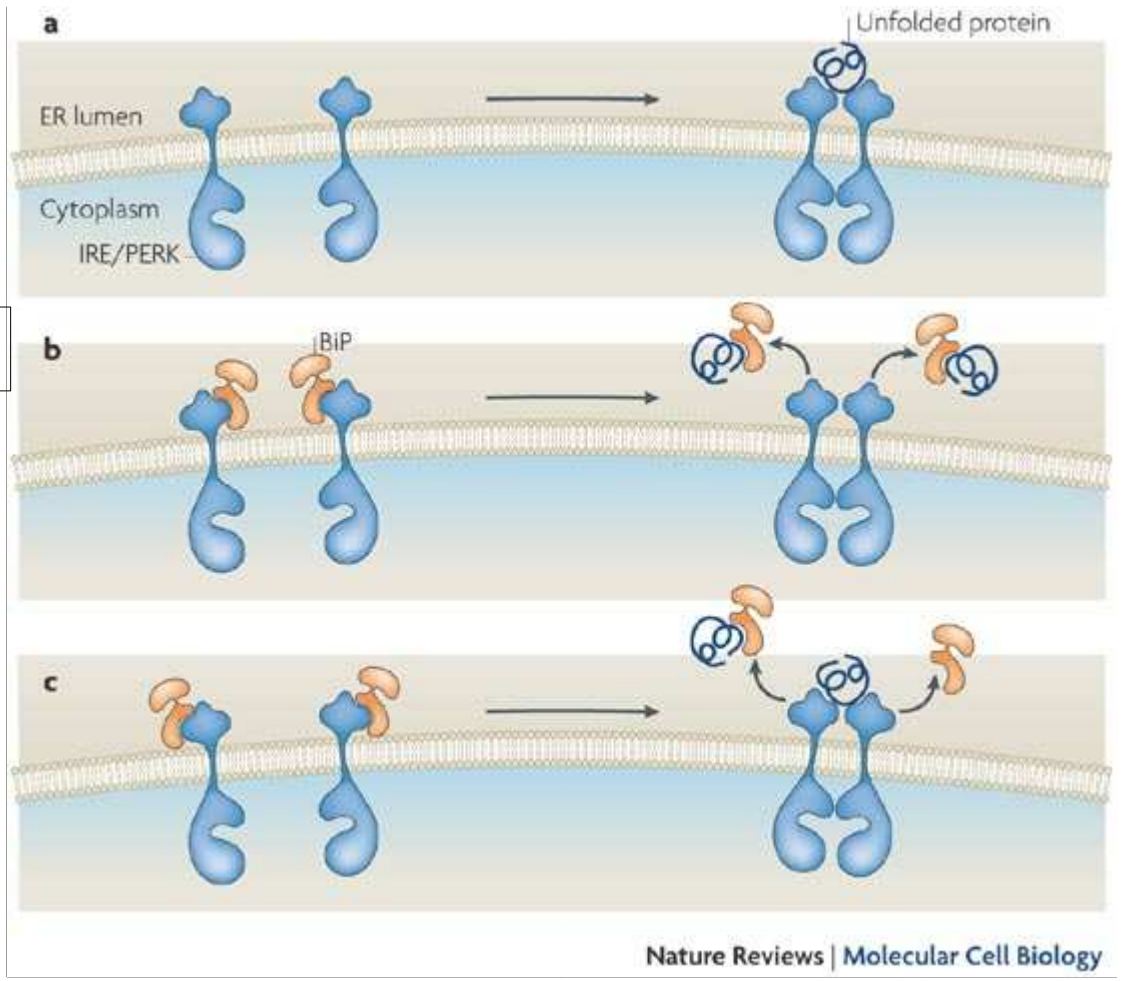
Proc. Natl. Acad. Sci. 2005; **102**:743-756

b. Indirect recognition model

Nature Cell Biol. 2000; **2**:326-332

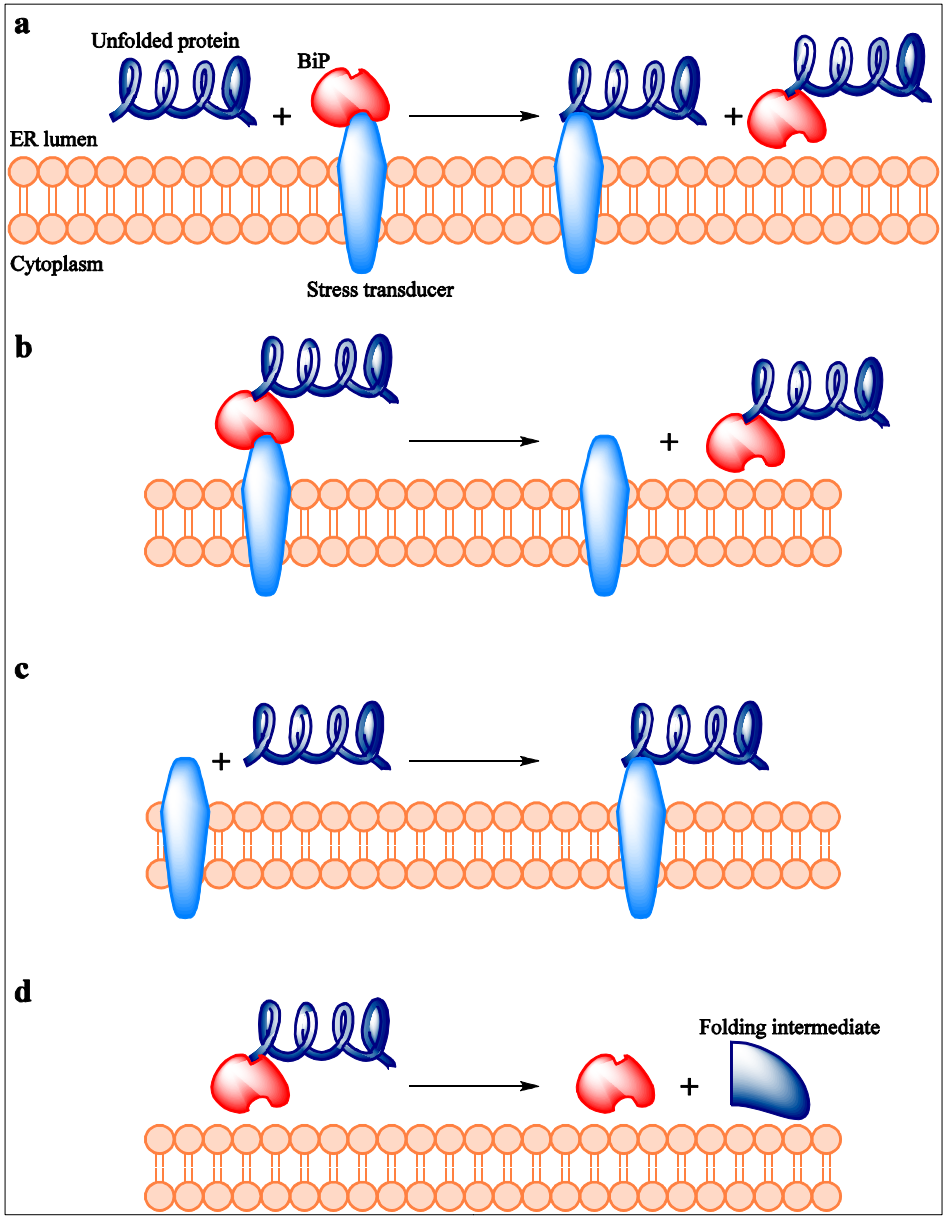
c. Hybrid recognition model

Mol Cell Biol. 2007; **8**:519-529

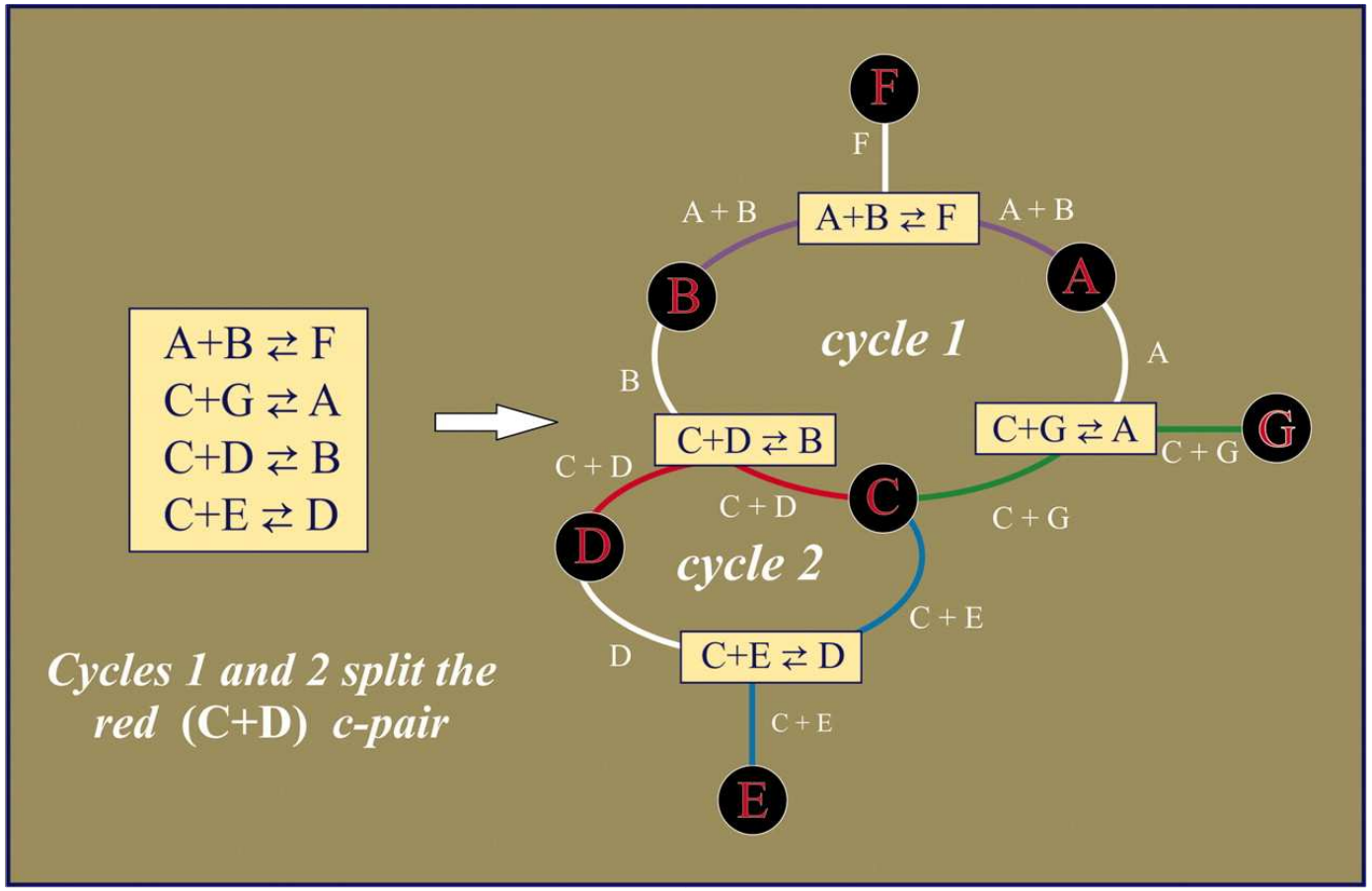


There are multiple interaction mechanisms for each model

Proposal for
Hybrid recognition model

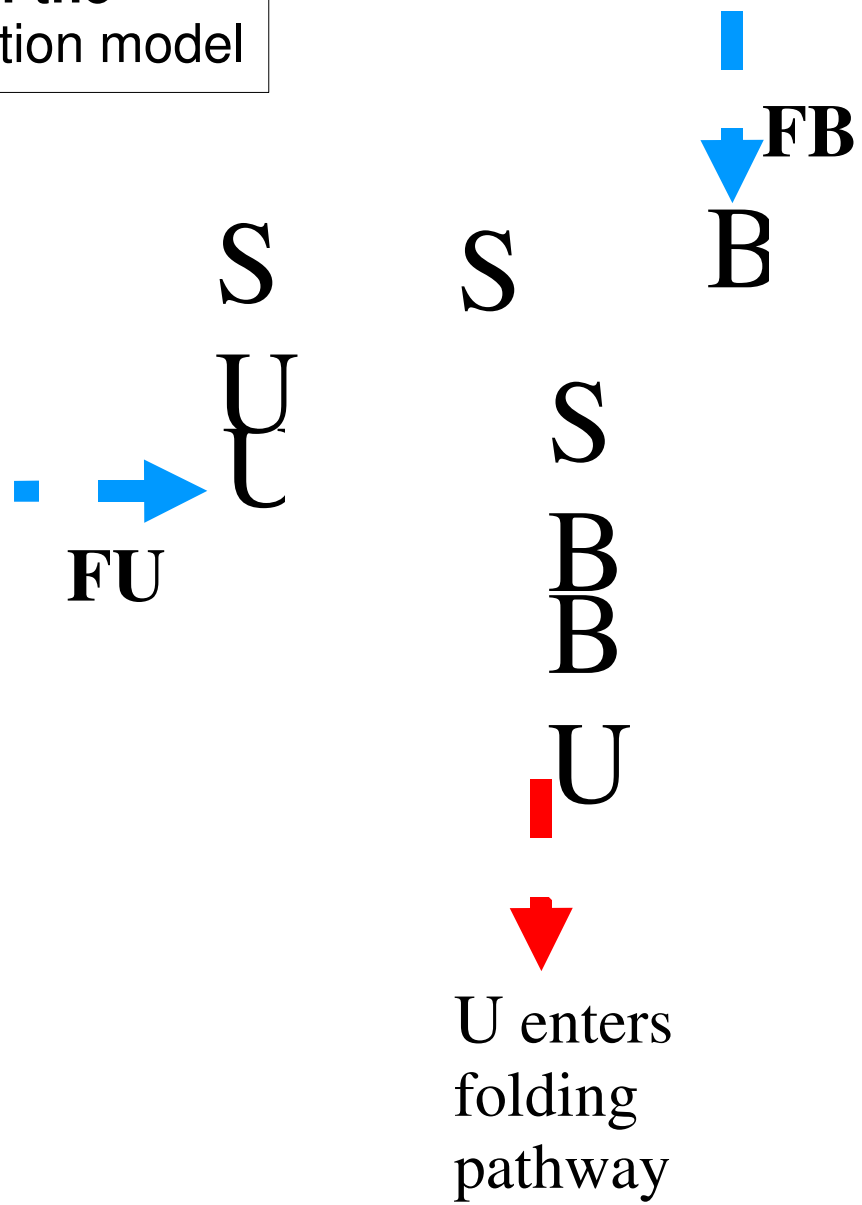


We explore the bi-stability of our enzyme-catalyzed reactions by investigating the cycle in the reaction

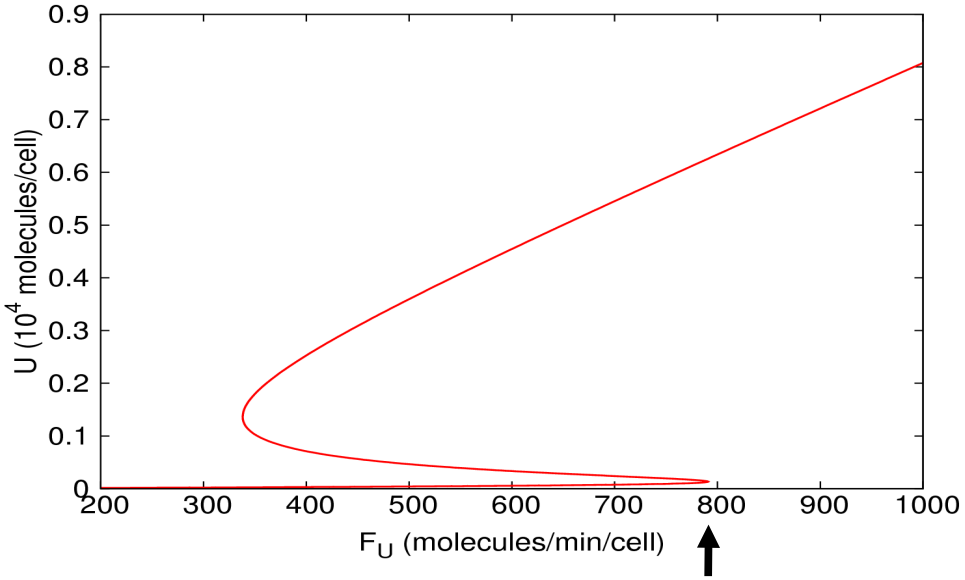


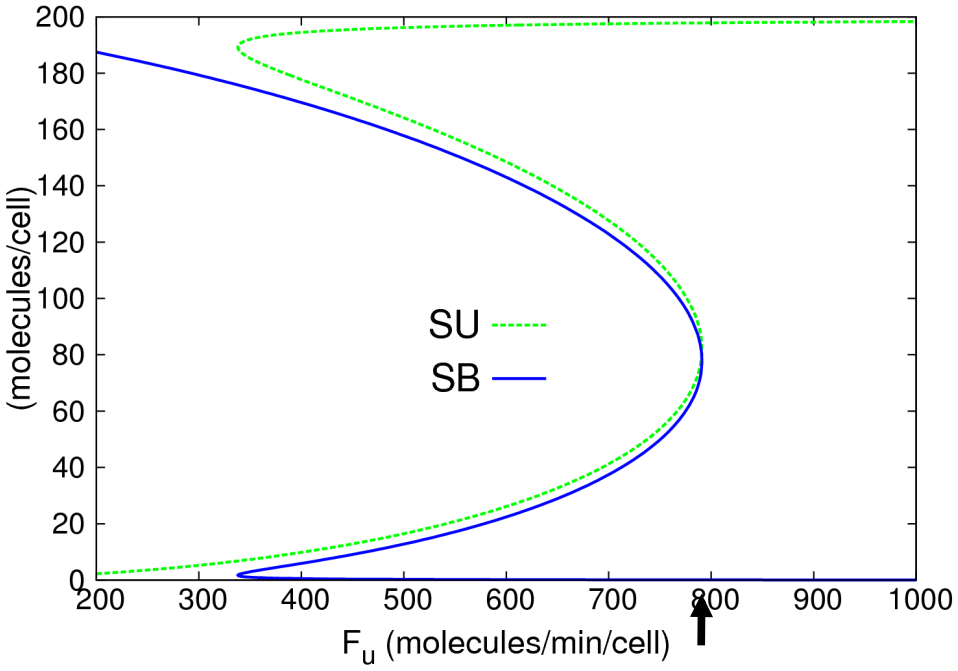
Craciun G. et.al. *Proc. Natl. Acad. Sci.* 2006;**103:**8697-8702

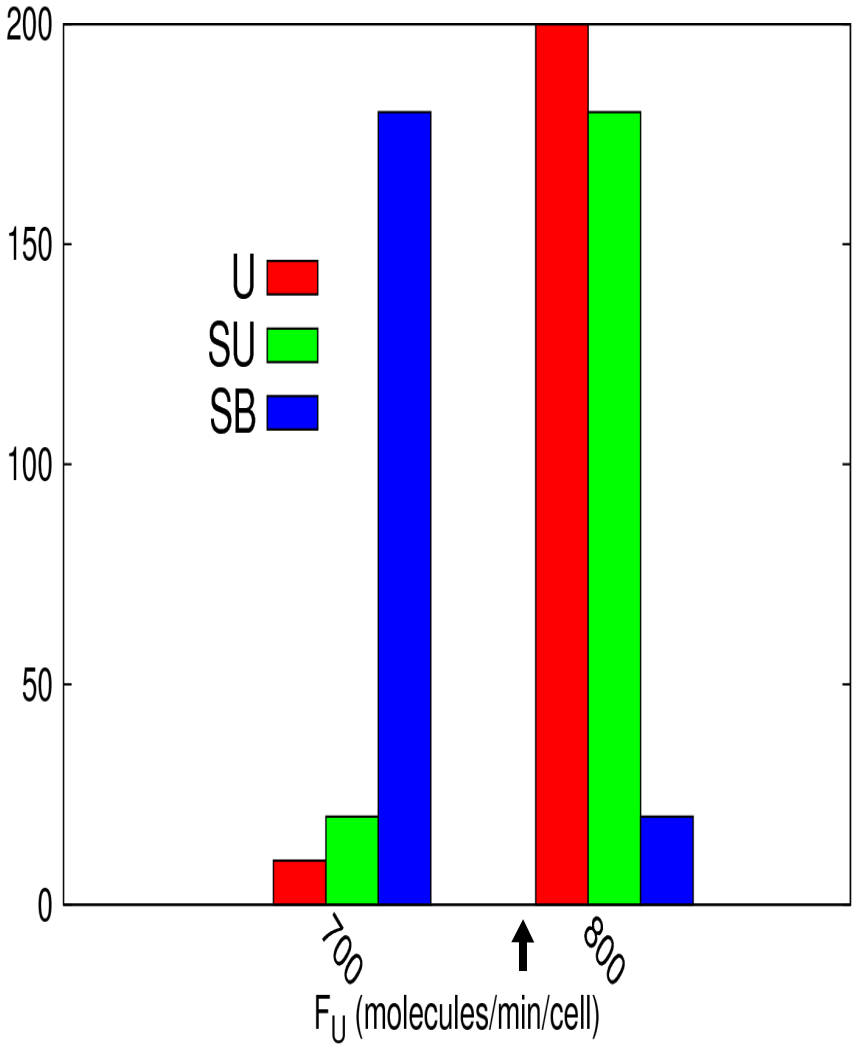
Our version of the
Hybrid recognition model



Our model shows that a subtle change in the influx of U can have substantial changes in the steady-state U protein density



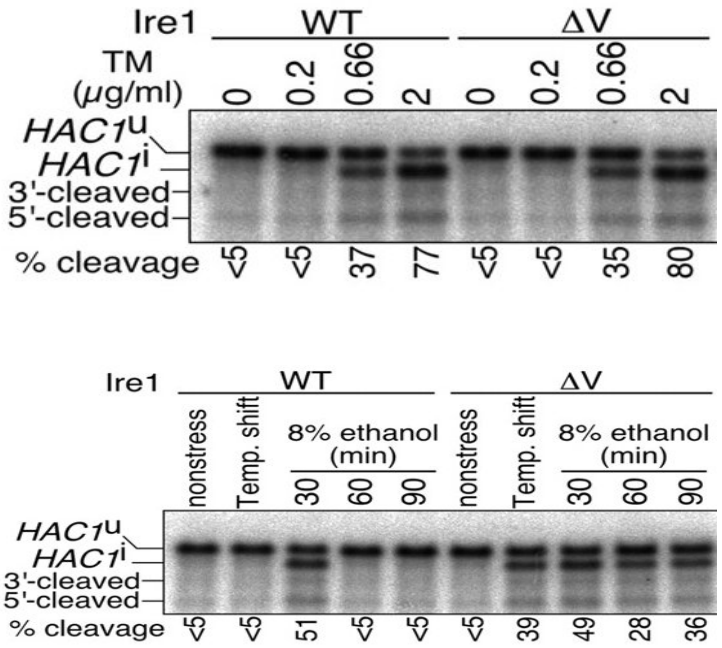




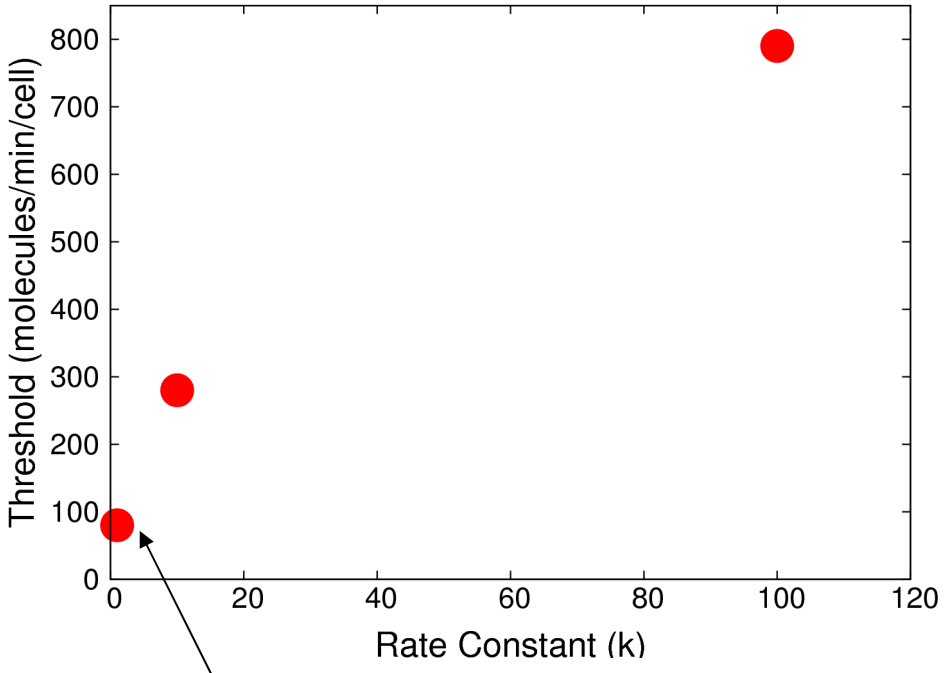
Our model also shows that BiP though is not essential for sensor activation it is essential for modulating the sensor activation

We simulate the "knock-down" of the S-B binding region letting k->0

J. Cell Biol. 2004; **167**:445-456

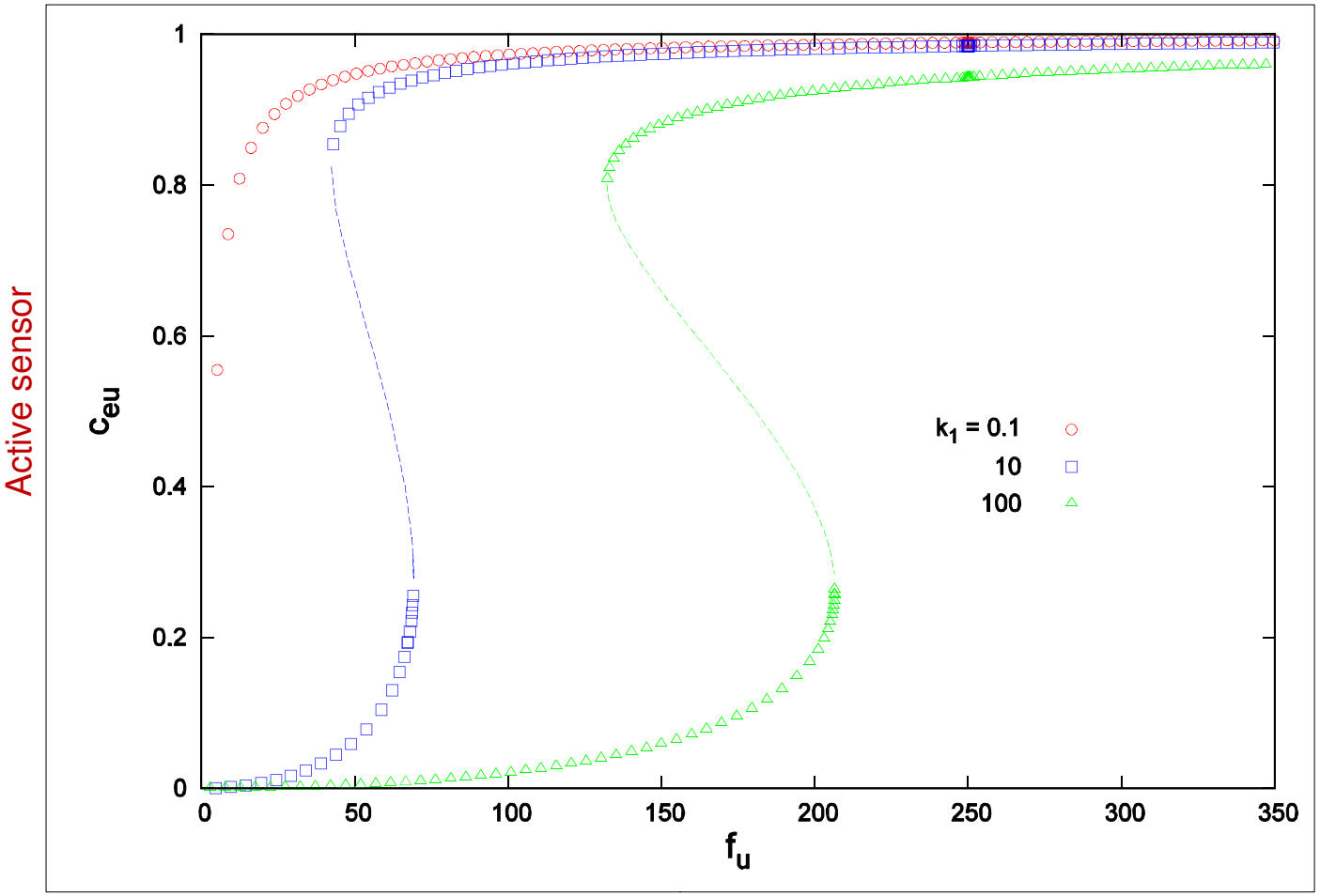


$$S + B \xrightarrow{k} SB$$

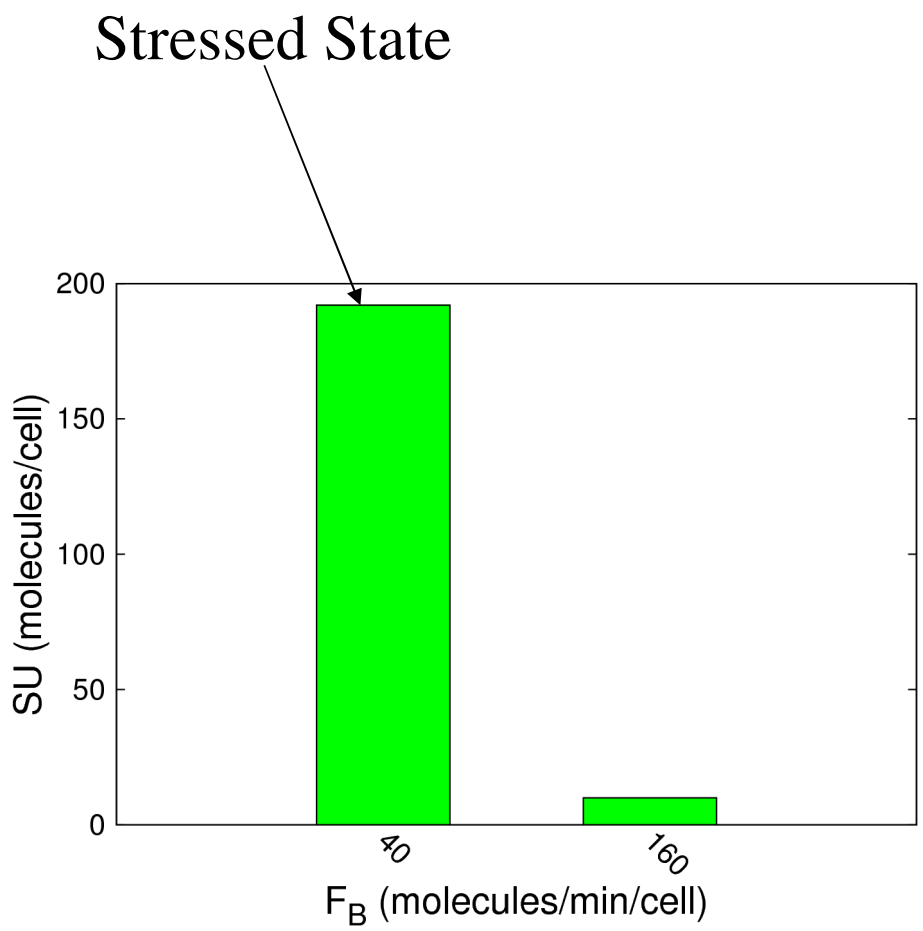


A lower threshold means the ER is stressed at a lower input of U

However, the absence of BiP can affects qualitative behaviour of the stress response



During the UPR, an increase in the BiP concentration will switch the steady-state of the sensor from the active to the inactive form

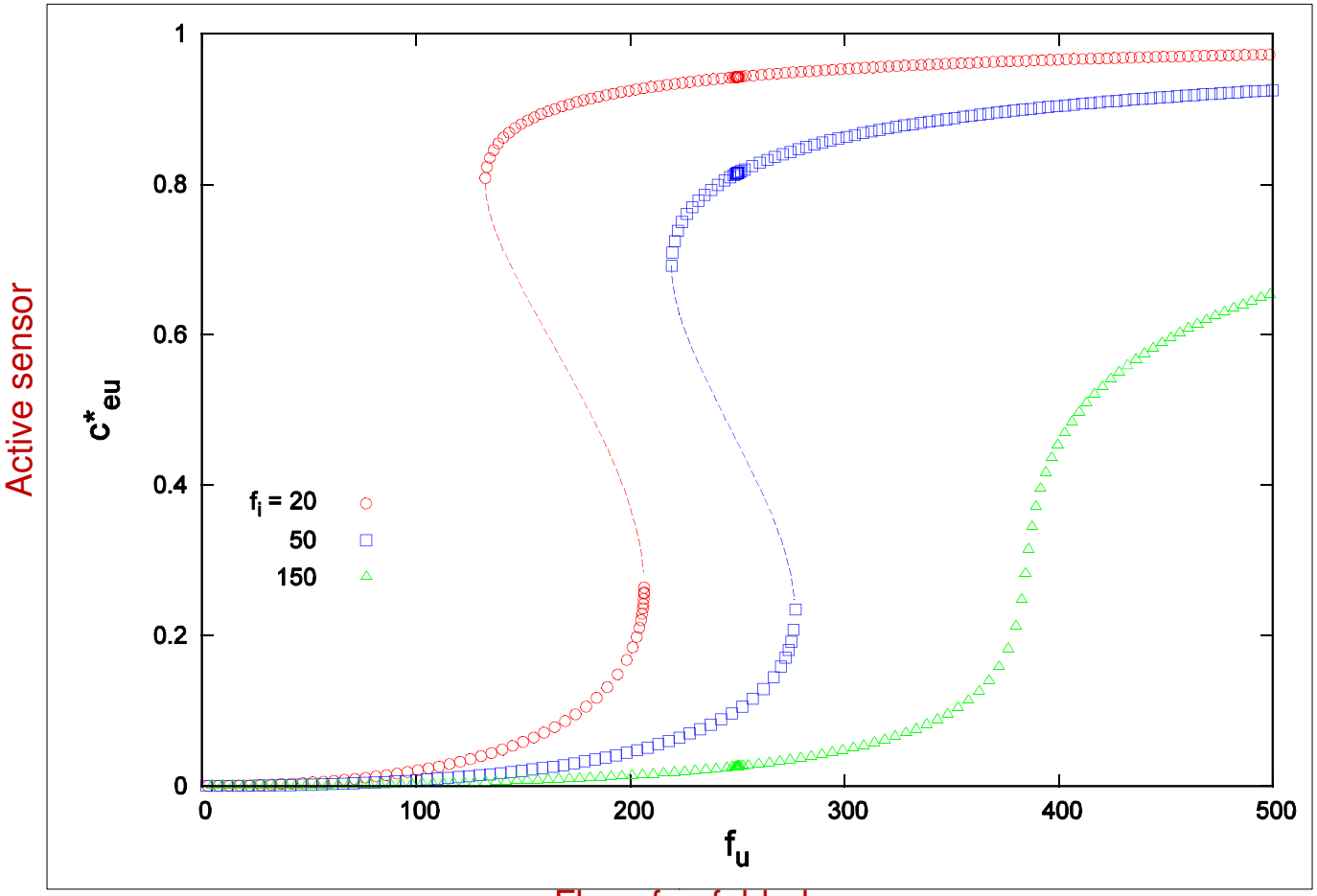


Flux of BiP

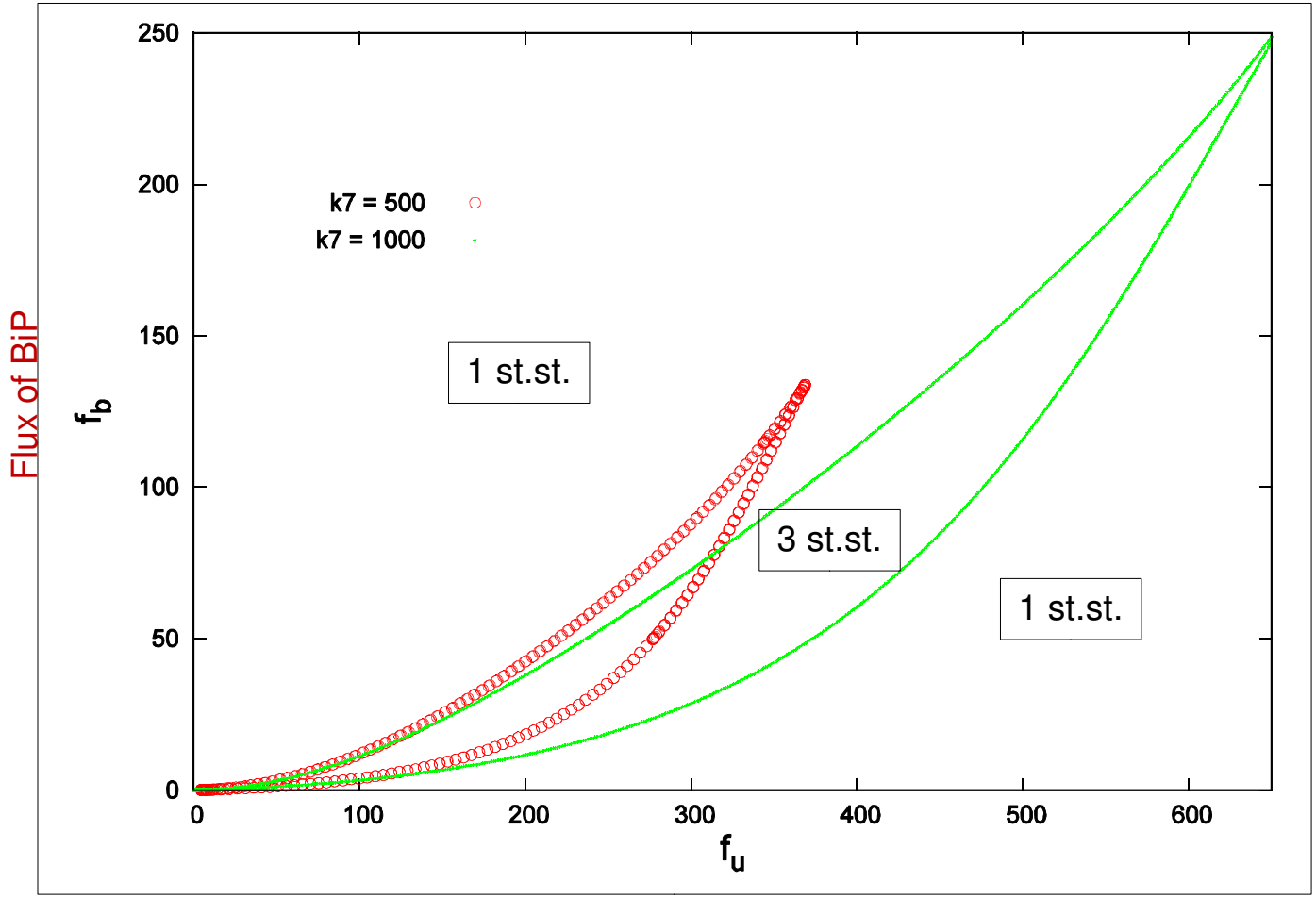
Flux of U is constant

The model predicts that increasing the amount of BiP in the ER lumen alliviates the stress.

Over-expression of BiP can lead to the inactivation of the UPR



We found that the most critical parameters for the bistable behaviour is the catalytic constant



Flux of unfolded protein

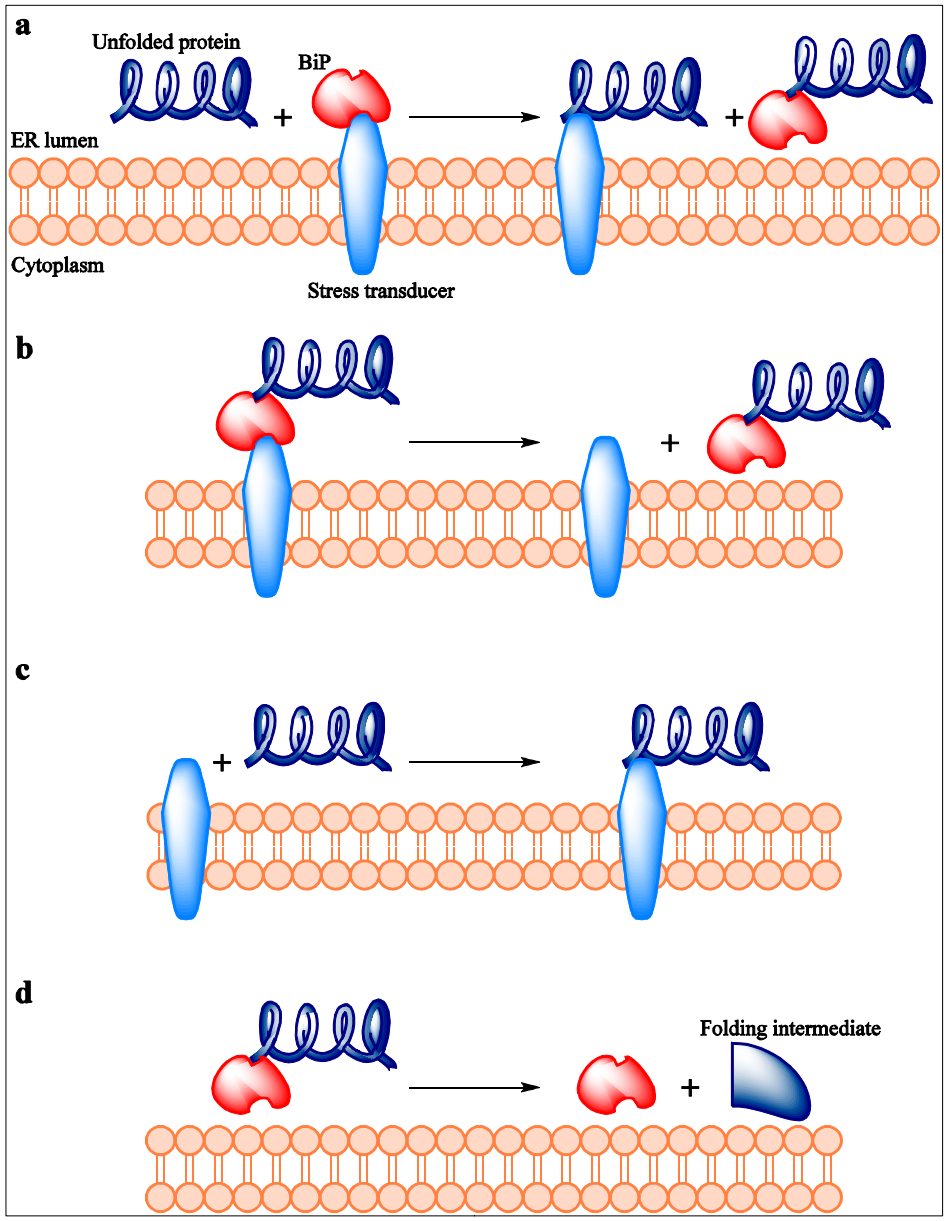
Summary

We found out that the sensing system is capable of a switch-like behaviour. ON-OFF states are separated by biologically improbable ones.

Chaperones, while a non-essential component in Unfolded protein sensing system, are down regulators of the UPR.

A proper change in the influx of chaperons can restore homeostasis. This is expected and nicely predicted by the model.

Where are we heading now?



Is this sensing mechanism robust?

If linked to the unfolded protein response pathways will model properly the proteotasis.

Can we use this model to make pharmacological predictions?