



THE ROCKEFELLER UNIVERSITY

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PRESIDENT

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Dear Professor Tsou:

I read with great interest your paper on protein folding that appeared in *Biochemistry*, March 22, 1988. Although I do not actively conduct research in this field, your letter raises issues that have been of very great interest to me for the past 30 years.

If folding is concurrent with translation I would expect that, as you say, post-translational adjustments would ensue to bring the completed chain into its final, lowest energy state.

I am going to raise a slightly different argument, however, about whether this final lowest energy state is the biologically active state. As you point out the approach to equilibrium from the renatured state may be a lengthy process and in principle there may be kinetic constraints that will require many hours or perhaps even virtually infinite time.

The plausible possibility that I then pose to you is that many proteins will be in their biologically active (and evolutionary selected) conformation for a period of seconds to minutes after translation is completed, but that they can then undergo further transitions to the thermodynamic limit, which is not necessarily biologically active. In that case there will have been many frustrations to protein chemists seeking to isolate proteins that retain their biologically active conformation, when the equilibrium conformer, stable after isolation and over long periods of storage, may well be biologically inactive. Certainly it is no part of the evolutionary process that protein products retain their most active conformation to suit the convenience of biochemists.

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an earlier
stage of
my speculation

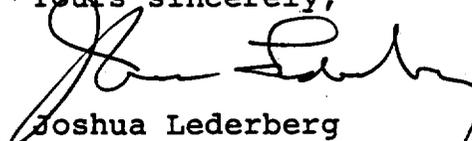
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What I don't know is whether there is tangible experimental evidence to support this conjecture. Do you know of isolations of purified proteins, preferably to crystallization, that have been demonstrated to be in a conformation that leaves them biologically inactive, although they have the same primary structure as the biologically active product of translation?

I am glad to see more attention given to the problem of folding, particularly in respect to its evolutionary implications. My own intuitive view is that the sequences we now observe in organisms are very stringently selected so as to permit folding to occur into a preferred conformer, in order to avoid the inefficiencies that would obtain if there were a wide variety of competing conformations that were kinetically accessible and were approximately in the same energy state. That is not inconsistent with the "protein-isolators dilemma" that I mentioned earlier in this letter.

Yours sincerely,



Joshua Lederberg

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