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Spontaneous Protein Denaturation as a Blind Spot in (Fish) Physiology

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Abstract

Spontaneous protein denaturation (SPD) occurs throughout the animal kingdom, with different proteins having half-lives ranging from a few days to months — even under benign conditions — due to unavoidable shocks caused by Brownian motion. Denatured proteins, i.e., proteins that have lost the 3-dimensional structure required for their function, e.g., as enzymes, must be re-synthesized, which requires adenosine triphosphate (ATP), and hence oxygen. Yet biochemistry textbooks, of which we examined 16 in 5 languages, present protein denaturation as an extraordinary phenomenon occurring under extreme conditions (high temperature, low pH, etc.) and fail to mention its universality and occurrence under even benign conditions. We argue — and present evidence — suggesting that the resulting neglect of SPD is an important reason why fish physiologists mostly ignore it, even when they deal, in their research, with temperature-induced increases of metabolic rates in fish. The resulting blind spot has serious consequences, as it leads to underestimating the impacts of the warming and deoxygenation of marine and freshwaters caused by global warming.

Full Text

Spontaneous protein denaturation (SPD) is ubiquitous in the animal kingdom, with different proteins having half-lives ranging from a few days to months (Dickinson 1985; Pauly and Lam 2023). Fully denatured proteins, i.e., proteins that have lost the structures required for their function (such as the 3-dimensional structure of some enzymes), become useless “random coils” (Smith et al. 1996) and must be re-synthesized. This process requires adenosine triphosphate (ATP) as a source of cellular energy, and its production through aerobic respiration ultimately depends on oxygen.

Most instances of denaturation are caused by the kinetic shocks produced by Brownian motion in the aqueous cytoplasm of living cells (Dickinson 1985). Indeed, it was the behavior of ‘small particles’ subjected to Brownian motion that Albert Einstein used to demonstrate the existence of molecules (Einstein 1905). Brownian motion is extremely sensitive to changes in temperature and may be viewed as the visible expression of the ‘heat’ of which temperature is a measure. Yet, despite the fundamental importance of temperature to animal physiology, and particularly to water-breathing ectotherms, the increased SPD that occurs when these animals are exposed to even slight increases in water temperature is rarely, if ever, considered in discussions of their physiology. The resulting increase in metabolic demand, and its potentially negative consequences for growth rate (Pauly and Lam 2023), are likewise rarely attributed to the temperature sensitivity of Brownian motion and the consequent increase in SPD.

This omission is particularly evident in the literature on fish physiology. For example, this elementary process is not mentioned in the 23,534 pages, 485 chapters, and 41 ‘volumes’ (and 47 actual books) of the prestigious *Fish Physiology* series, mainly edited by physiologists of the Department of Zoology at the University of British Columbia. Similarly, among the 160 journal articles and book chapters commenting. in Lopez-Ahedo and Pauly (2026) on three papers by the first author of the present

contribution, only one mentions SPD (Lavin et al. 2022). This is despite SPD being explicitly considered as a key component of the hypotheses in two of the papers in question (see Supplementary Information). This non-consideration of SPD by biologists, and specifically by fish physiologists, demands an explanation.

This explanation may be found in the manner in which biochemistry textbooks, from which most physiologists learned as students, present denaturation. Rather than presenting it as a process that occurs continuously in all living cells, with its intensity varying under normal conditions and particularly with temperature in poikilotherms, textbooks commonly present denaturation as a process that occurs under extreme conditions. Examples include the high temperatures required to boil an egg, a favorite example in many of the 16 biochemistry textbooks in five languages that we examined, or exposure to very low pH (see Supplementary Information). A few textbooks do mention that SPD can also occur under benign or 'normal' conditions. However, they do not make the connection between SPD and Brownian motion, nor do they mention the extreme sensitivity of this process to changes in temperature.

We believe, therefore, that this manner of presenting denaturation in biochemistry textbooks over more than 50 years has created a major blind spot in physiology, notably concerning the metabolism of water-breathing ectotherms. This blind spot, we fear, has led to the non-consideration of SPD as a major cause of the increased oxygen demand of fish exposed to even small increase of temperature, as manifested in their increased metabolic rate. This leads to an underestimation of the effects of ocean and freshwater warming and deoxygenation by physiologists, i.e., the very researchers who should be able to evaluate the devastating environmental conditions that warming and deoxygenation this will impose on water-breathing animals.

Declarations

Author Contribution

D.P. drafted the submission and some of the Supplementary Information and E.P. drafted most of the Supplementary Information. C. L. drafted the part pertaining to Chinese textbooks. All authors reviewed the manuscript.

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