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Why human milk is more nutritious than cow milk

Niels Voorhoeve [a], Douglas C. Allan [b], M.A. Moret [c], G.F. Zebende [d], J.C. Phillips [e,*]

[a] Sound, Washington, DC, USA
[b] Corning Inc, Div. Sci. & Technol., Corning, NY, USA
[c] Univ Estado Bahia, Salvador, BA, Brazil
[d] Univ Estadual Feira de Santana, Brazil
[e] Rutgers Univ., Piscataway, NJ, USA

HIGHLIGHTS

- Casein proteins assemble to form micelles, which deliver calcium to bones and teeth.
- Individual caseins do not crystallize, so their molecular structure is unknown.
- Thermodynamic scaling exploits self-organized criticality in protein amino acid sequences.
- Most proteins evolve little within mammals, while casein evolution is very large.
- Critical features of casein dynamical synchronization occur in many other proteins.

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ABSTRACT

The evolution of milk, the key infant nutrient, is analyzed using a novel thermodynamic molecular method. The method is general, and it has many advantages compared to conventional molecular dynamics simulations. It is much simpler, and it connects amino acid sequences directly to function, often without knowing detailed "folded" globular structures. It emphasizes synchronized critical fluctuations due to long-range correlations in globular curvatures. The titled question has not been answered, or even discussed successfully, by other molecular methods.

1. Introduction

The evolutionary change from a gland secretion to milk involves an increase in calcium and protein concentrations by up to 100- and 1000-fold, respectively. Such an abrupt change seemed unlikely to 19th century opponents of Darwinian evolution [1], but today we recognize that Darwinian selection probably occurs by exchange of modular genetic fragments [2]. We can go much further by assuming that evolution improves protein functions by bringing them closer to thermodynamic critical points ("perfect functionality"). This has led to specific results for many proteins, including several of immediate biomedical interest [3]. Here we discuss the evolution of milk from mice to cows to humans. The analysis confirms the modular model, and shows how milk has evolved as the key infant nutrient. It seems likely that it is nearly optimized in humans [4].

* Corresponding author.
E-mail address: jcphillips8@comcast.net (J.C. Phillips).

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Protein amino acid sequences, viewed collectively for all proteins, form a data base which in principle may contain threads of modular structure with universal character. Protein chains usually fold into globules, and such globules may have characteristic curvatures that depend both on their amino acid sequences and their dominant interactive environment, which is usually close to cellular membranes. The key feature of such globules is that the amino acid side groups of protein chains have a range of interactions with water, from hydrophobic to hydrophilic [4]. Alternating chain regions thus fold inwards for hydrophobic regions, and outwards for hydrophilic ones. Globular extrema in Euclidean space should be related to hydropathic extrema, especially through in/out extrema of functional (long-range conformational) excitations. These are associated with changes in surface shape, and especially the hydrogen-bonded water–amino acid interfacial free energy E, changes of which determine small and reversible functional free energy changes. Associated with this interfacial energy E are changes in the hydrophob(phil)ic extrema in protein in(ex)teriors (analogous to dynamically balanced repulsive (attractive) interactions in the van der Waals equation of state [3]).

During the "classic" biomolecular theory period (before 2000), more than 100 hydropathicity scales were proposed [3], but all of them were based on solvent short-range interactions with individual amino acids (length scale $L = 1$). A major breakthrough occurred in 2007 in Brazil, where Moret and Zebende (MZ) discovered that a log–log plot of solvent accessible surface areas of modular protein segments containing amino acids with $9 \leq L \leq 35$ is linear for all 20 amino acids (aa) at the center of each of >5000 analyzed segments [5]. This confirmed several long-standing conjectures involving the collective evolution of fundamental water–protein interactions, viewed in the context of self-organized thermodynamic criticality [3,6,7]. The linearity reflects power-law functions, and the powers (log–log linear slopes) Ψ(aa) are called fractals. Fractals characterize 2nd order phase transitions, and thus prove protein thermodynamic criticality [3]. Protein-specific functional modularity is included by averaging Ψ(aa) over a segment of length W to obtain Ψ(aa,W), which can be used to find presumed lengths W^* of modular conformational excitations from the resting state to the dominant metastably active functioning state.

Thermodynamic models are sometimes used in connection with Newtonian molecular dynamics simulations (MDS) to estimate protein kinetics, but this has never been done for subtle evolutionary developments of specific proteins. MDS studies specific structures associated with static resting or ground states dynamically in order to estimate excitation energies statically, but this is feasible only when the excited states involve only large motions of a few atoms (short-range interactions only). Nearly all proteins have a globular structure, regardless of whether their secondary structure is absent (disordered proteins); an interesting exception is p53, which has a starfish structure [3]. Most proteins' conformational functionality is spread efficiently over most of the globular surface and core, and such excitations spanning thousands of atoms (long-range many-body interactions) are not easily identified by MDS. Experience with many proteins has shown [3,8] that the fractal scale [5] accurately describes the evolution of dynamical features of proteins near thermodynamic critical points through Ψ(aa,W^*) modular profiles with large W^*. Its evolutionary successes demonstrate the benefits of its much greater accuracy [3]. Comparisons with the standard 1982 scale, based on first-order unfolding (too large and not reversible), usually show greater accuracy of the Moret and Zebende scale [3].

2. Beta-casein

A given protein's function(s) should depend on optimized value(s) of $W = W^*$, so to proceed one must determine W^*. Most often this is done from the evolution of the protein's globular curvatures, whose average changes are usually monitored by the overall relative amplitudes of the oscillations of Ψ(aa,W) profiles [3]. Our first example here is β casein and its mouse (231 aa), bovine (224 aa) and human (226 aa) amino acid sequences. The BLAST positives for bovine and human are 66%, which suggests that they share a common fold. The β-casein fraction of human milk comprises more than 85% of total casein, whereas the β-casein fraction of bovine milk is much lower (33% of the total casein) [9]. Thus evolution has rebalanced the casein fractions, and we will see how this rebalancing is described by comparing casein Ψ(aa,W^*) profiles.

The average curvatures are related to the variances (mean square fluctuations) of Ψ(aa,W). The basic idea is that for the protein chain to fold stably and refold reversibly, the interior regions must be clearly distinguished from the exterior or surface regions. The interior (exterior) regions are predominantly hydrophob(phil)ic. Because the chain is so long, each modular region will contain on the average W amino acids. The overall differences between the two sets of regions will increase with the variance, which is a standard statistical tool, and which measures the oscillation amplitudes of Ψ(aa,W) profiles. For $W > 10$, human proteins usually have the largest or smallest variances, and for β casein they are the largest. Thus we show in Fig. 1 the variance ratios human/bovine and human/mouse of Ψ(aa,W) as functions of W. There is an unambiguous peak at $W = W^* = 37$ (the upper limit of [5]'s fractal range). This peak represents the conformational wave length that evolution has optimized from bovine to human β casein. Here and in other proteins [3], optimizing W magnifies interspecies differences, and resolves important aspects of functional evolution.

Now that we know $W^* = 37$ in β casein (and not 1 or 5 or some other small number appropriate to short-range interactions), we can use Web-based sequence alignment (BLAST) to compare the hydropathic profiles of mouse, bovine and human (Fig. 2). Their similarities and differences are easily seen, whereas BLAST is unable to align entire mouse with human or bovine sequences. The profiles can be informative to observers previously unacquainted with molecular thermodynamics; moreover, they echo features already found in other well-studied proteins, such as hen egg white and myoglobin [3]. Hydrophilic minima function as surface hinges for large-scale conformational motions involved in reversible protein functions, while hydrophobic maxima are core pivots for these motions [3]. According to Fig. 2, the largest change