

Mini review

# Misfolded Protein Molecules as Added Dimensions of Generic Performance Dynamics of Neuronal Function and Dysfunction

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## Abstract

Performance neuronal dimensions include the realization of attribute formulation in terms of folded molecules with a specifically targeted landscape of protein misfolding. Misfolding patterns of molecular structure perform proportional identity reformulation in terms of ongoing systems for re-appraisal of free energy levels with solute-solvent dimensions. The promotional re-creation for misfolding is integral to the parent attributes of folding and refolding that carry considerable reconstitution patterns of disease establishment and progression. Emergent patterns of aggregating dynamics perform the series of accumulated intermediate protein forms within the system profile determinations of consequential cooperative phenomena for protein molecular misfolding and accumulation within cells and tissues such as the central nervous system.

## Introduction

The generic dynamics of the folded versus unfolded protein three-dimensional conformation introduce an overall series of systems that obligate consideration of thermodynamic principles. Bound flexibility of backbone systems of such proteins contribute to perspective degrees of entropy configuration on the one hand and enthalpy pathway interactivities with the surrounding solvent molecules. The overall constitutive forces of configuration of the protein molecule allow for the hydrophobicity and hydrogen bond dynamics that operate to induce an autonomous re-figuration of molecular dimensions. Small heat shock proteins in particular attenuate mitochondrial dysfunction and reduce the accumulation of misfolded proteins and thus exert neuroprotective effects in neurons [1]. Cross-seeding of misfolded amyloid proteins appears to induce cross-species infection in prion diseases [2]. Gain-of-toxicity mechanisms develop as accumulation of aggregation-prone conformers of misfolded cellular proteins in general [3].

Comparative reconstitution involves an intermediate series of molecular structure that arises as direct result of the primary amino acid sequences of the protein. In terms

of ongoing productivity and re-dimensionalization, it is particularly significant to view the attributes of such measures as also persistent degrees of flexibility of the protein core structure that promotes further configuration patterns as well illustrated by the landscape energy concepts.

Proteins fold in the time scale of microseconds to milliseconds; utilising the Master equation, the Mean First Passage Time to acquire the misfolded conformation from the native or folded state is independent of the protein length, the number of native contacts and the rate constant for the misfolded to the folded state [4]. The degrees for promotional energy production and utilization of molecular reconfiguration create a permissive micro-environment as contextualization that allows for dynamics of molecular rephrasing and release of entropic configuration. The proteasome is an excellent object of study in elucidating the mechanisms and roles of protein-protein interactions at many levels [5].

## Folding Patterns

Protein folding is inherently error prone and changes

in amino acids, altered post translational modifications and cellular stress can induce protein misfolding [6]. Patterns of further phenomena allow for the concept of trapping of intermediate molecular misfolding within the system dynamics of aggregation of various related molecular species. Dysfunction of organelles protein quality control machinery promotes protein misfolding associated with cardiovascular, neurodegenerative, metabolic and secretory disorders [7]. In such manner, proportional recapitulation of the three-dimensional forms of a biophysical model of the protein would indeed promote systems of repeated reconfiguration as support of the central dogma of molecular biology that is further characterized by dimensional reconstitution of the 3-dimensional field of funnel-shaped proportions.

The process of protein quality control followed by proteasomal elimination involves an intricate interplay between the endoplasmic reticulum and the cytosol [8]. Patterns of molecular reconfiguration permit the molten globule parameters of folding within the further considerable proportions of reformulation as added dimensions for further potential folding dynamics. Misfolding of the normal prion protein into disease-associated PrPSc is the critical etiologic event underpinning prion diseases [9].

In such cases, the overall generic parameters of folding include a strong diversity range for misfolding of the protein molecule in terms of ongoing hydrophobicity forces within the central intra-molecular core of the protein. The endoplasmic reticulum in stress conditions due to accumulated misfolded/unfolded proteins contributes to progression of several disorders including neurodegeneration [10]. In the various contexts that promote a permissive series of patterned reconstitution there arise system patterns for further misfolding as well projected within the pathway progressive steps of autonomous folding.

### Amino Acid Sequence

Patterns of encoded sequence homology function within the flow dogma proceeding from DNA to protein molecular dimensions of both folded and misfolded forms of established formulation. Trapped misfolded model structures permit a series of accumulative forms of the three-dimensional structures to include persistent re-modulations that target an end-stage irreversibility of the folded molecule.

The molecular chaperone Hsp90 participates in protein folding, directs misfolded proteins for degradation and is involved in regulating cellular transcriptional responses to environmental stress [11].

In such terms, ongoing interactive forces at the surface of the molecular structure include the interactivities of the side-chains, as well-borne out by the progression of permissive environmental patterns of cooperative

action. The luminal domain of the endoplasmic stress sensor protein PERK binds misfolded proteins and hence triggers PERK oligomerization and activation resulting in ER stress signaling and the unfolded protein response [12]. The chaperones and supporting molecular systems include the dimensions for further ongoing re-folding patterns. The small heat shock protein Hsp27 binds alpha-synuclein fibrils, preventing elongation and cytotoxicity [13]. Toxicity of mutant SOD1 appears to result from its misfolding. Macrophage migration inhibitory factor has cytokine/chemokine activity and cytosolic chaperone-like properties that inhibit the accumulation of misfolded superoxide dismutase in amyotrophic lateral sclerosis [14]. The end-stage promotional configuration is accounted for by the refolded trapping measures as well-illustrated by the landscape-energy dimensions.

Proportional biology of systems permits consideration of the further promotional attributes for re-folding within the patterned reconstitution, as well-documented intermediate forms that are displayed by simulation studies of molecular configuration.

Aggregation is a consequence of both intra-cellular and extra-cellular proportions, further confirmed by dimensions of cooperative phenomena of constitutive origin and progression. Chaperones with aggregate activity promote and organise the aggregation of misfolded proteins and their deposition at specific intracellular sites [15]. Incremental creation and utilisation of Gibbs free energy sources are patterns of ongoing attempts at resolution of the three-dimensional configuration that further promote systems of molecular patterns.

### Misfolding Performance

The molecular structure of a given molecule is dimensional reconfiguration within pathways that are indeed promotional events in misfolding per se. it is towards the dimensional portrayal of proportional consideration that misfolding of the protein molecule allows for consideration of both intra-molecular and inter-molecular forces that promote the emergent permissiveness of three-dimensional reconstitution attempts. Misfolded alpha-synuclein serves as a template and induces misfolding of endogenous alpha-synuclein with oligomer formation that progresses to fibrils and Lewy bodies; misfolding of alpha-synuclein confers prion-like properties enabling its spread from cell to cell [16].

Persistence of patterned permissiveness confronts the sequential dominance of amino-acid constitution of a given protein, as well-illustrated by dimensions of the disulfide bonds in establishing and reconstituting molecular folding dynamics. Proportional diversity is best viewed within the systematic parameters of amyloidogenesis and of particle collision dimensions in molecular sequence re-localization. Misfolded proteins appear to

constitute not only markers but also active carriers of pathogenicity [17]. Parameters of progressive interactivity of side-chains as strictly polar dimensions include distributional dynamics for further chain formation as constituted in terms of a paradoxical series of misfolding steps.

### Molecular Projection

Molecular projections allow for the emergence of patterns of attempted resolution in terms of ongoing performance attributes bound to the outlined interactivity patterns both intra-molecularly and inter-molecularly. Both acute proteotoxic stresses that unfold proteins, and expression of disease-causing mutant proteins that expose aggregation-prone regions, can promote protein aggregation; coating of protein aggregates by Hsp70 chaperones constitutes the conserved initial step [18]. The performance dynamics of misfolding promote permissiveness as additional patterns of reconstituted misfolding. The series of attribute dimensions include the role-patterns for misfolding within the added reformulation of an end-stage of irreversibly folded molecular patterns of resolution.

Models of interactivity of protein molecular folding patterns include the eventual establishment of misfolding in terms of utilization reformulation that includes numerous molecular traps and dimensional re-folding. Accumulation of unfolded or misfolded proteins in the endoplasmic reticulum (ER) lumen promotes ER stress that is related to cellular reactive oxygen species production [19]. The degrees of proportional cooperation within dimension landscapes and fields of dynamic turnover include dimensional reconstitution of many intermediate molecular forms as well-projected by energy levels of entropy. The further cooperative attributes for additional re-folding is hence a highly permissive micro-environment within system patterns of consequential reconstitution, as indeed realized by mutant forms of the given protein molecule. Structural conversion of diffraction-limited aggregates of misfolded proteins correlates with the potential for aggregates to disrupt lipid bilayers [20].

### Constitutive Performance

Performance dynamics are a clue to the structural homologies of a given protein in terms of function of various molecular forms in such disorders as aggregation phenomena in Alzheimer and Parkinson's disease. Equilibrium of protein moieties, that are situated intra-cellularly and extra-cellularly, allows for the performance profile dynamics that include membrane performance as attribute dimension in patterned folding and patterned misfolding. In such terms, ongoing reconfiguration of protein molecules includes energy landscapes as perfor-

mance dimensions in molecular folding and misfolding.

### Concluding Remarks

Dimensionalization includes the projected proposals for further folding as terms that are often defined by dynamics of misfolded protein molecules. It is further to be considered the trapped moiety forms of intermediates created by dynamics of misfolding. The terrain dimensions in energy landscape maps and of persistent accumulation of such abnormal molecular forms allow for consideration of protein molecular dynamics as integral to functionality of the given molecule. Patterns of constitutive determination by the sequence profile of amino acids allows for further conformational resolution in terms of system identity and as pathways of projected dimensions in terms of further attempts at reconstitution of energy supply and resource. Various degenerative disease of the nervous system portrays the dimensional resolution of protein aggregates that accumulate specifically both in terms of the intra-cellular dimensions and as extra-cellular profiles of attempted resolution of the three-dimensional protein moiety.

### References

1. Zhu Z, Reiser G. The small heat shock proteins, especially HspB4 and HspB5 are promising protectants in neurodegenerative diseases. *Neurochem Int.* 2018.
2. Yoo BK, Xiao Y, McElheny D, et al. E22G pathogenic mutation of beta-amyloid (A $\beta$ ) enhances mis-folding of A $\beta$ 40 by unexpected prion-like cross talk between A $\beta$ 42 and A $\beta$ 40. *J Am Chem Soc.* 2018.
3. Thellung S, Scoti B, Corsaro A, et al. Pharmacological activation of autophagy favours the clearing of intracellular aggregates of misfolded prion protein peptide to prevent neuronal death. *Cell Death Dis.* 2018; 9(2):166.
4. Singh V, Biswas P. Estimating the mean first passage time of protein misfolding. *Phys Chem Chem Phys.* 2018.
5. Gaczynska M, Osmulski PA. Targeting protein-protein interactions in ubiquitin-proteasome pathway. *Adv Protein Chem Struct Biol.* 2018; 110:123-165.
6. Shin YJ, Vavra U, Veit C, et al. The glycan-dependent ERAD machinery degrades topologically diverse misfolded proteins. *Plant J.* 2018.
7. Sharma R, Pramanik MMD, Chandramouli B, et al. Understanding organelles protein folding capacities and assessing their pharmacological modulation by small molecules. *Eur J Cell Biol.* 2018.
8. Berner N, Reutter KR, Wolf DH. Protein quality control of the endoplasmic reticulum and ubiquitin-proteasome-triggered degradation of aberrant proteins: Yeast pioneers the path. *Annu Rev Biochem.* 2018.
9. Taufiqul Islam AM, Adiard PA, Finkelstein DI, et al. Acute neurotoxicity models of prion disease. *ACS Chem Neurosci.* 2018.
10. Abdullah A, Ravanan P. Kaempferol mitigates endoplasmic reticulum stress induced cell death by targeting caspase 3/7. *Sci Rep.* 2018; 8(1):2189.
11. Neckers L, Blagg B, Haystead T, et al. Methods to validate Hsp90 inhibitor specificity, to identify off-target effects, and to rethink approaches for further clinical development. *Cell Stress Chaperones.* 2018.
12. Wang P, Li J, Tao J, et al. The luminal domain of the ER stress sensor protein PERK binds misfolded proteins and thereby triggers PERK

- oligomerization. *J Biol Chem*. 2018.
13. Cox D, Whiten DR, Brown J, et al. The small heat shock protein Hsp27 binds alpha-synuclein fibrils, preventing elongation and cytotoxicity. *J Biol Chem*. 2018.
  14. Shvil N, Banerjee V, Zoltzman G, et al. MIF inhibits the formation and toxicity of misfolded SOD1 amyloid aggregates: implications for familial ALS. *Cell Death Dis*. 2018.
  15. Grousis T, Ungelenk S, Miller S, et al. A prion-like domain in Hsp42 drives chaperone-facilitated aggregation of misfolded proteins” *J Cell Biology*. 2018.
  16. Liddle RA. Parkinson’s disease from the gut. *Brain Res*. 2018.
  17. Fandrich M, Nystrom S, Nilsson KPR, et al. Amyloid fibril polymorphism—a challenge for molecular imaging and therapy. *J Intern Med*. 2018.
  18. Mogk A, Bukau B, Kampinga HH. Cellular handling of protein aggregates by disaggregation machines. *Mol Cell*. 2018.
  19. Ge Y. Co-regulation of ER stress and oxidative stress in neuropathic pain and disinhibition of the spinal nociceptive circuitry. *Pain*. 2018.
  20. Varela JA, Rodrigues M, De S, et al. Optical structural analysis of individual alpha-synuclein oligomers. *Angew Chem Int Ed Engl*. 2018.

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