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Comparison of NMR structural and dynamics features of the urea and guanidine-denatured states of GED

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ABSTRACT

Denatured states of proteins, the starting points as well as the intermediates of folding in vivo, play important roles in biological function. In this context, we describe here urea unfolding and characterization of the denatured state of GTPase effector domain (GED) of dynamin created by 9.7 M urea. These are compared with similar data for guanidine induced denaturation reported earlier. The unfolding characteristics in the two cases, as measured by the optical probes, are significantly different, urea unfolding proceeding via an intermediate. The structural and motional characteristics, determined by NMR, of the two denatured states are also strikingly different. The urea-denatured state shows a combination of α- and β-preferences in contrast to the entirely β-preferences in the guanidine-denatured state. Higher $^{15}N$ transverse relaxation rates suggest higher folding propensities in the urea-denatured state. The implications of these to GED folding are discussed.

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Denatured states of proteins are beginning to be recognized as important entities in the biological world—a denatured state of a protein is defined as the lowest energy 'non-native' state under a given set of conditions [1]. Inside a living cell, the environmental conditions like local intracellular ion concentrations, interaction with various ligands etc. can vary significantly from organelle to organelle [2], and even within the same organelle there can be variations due to signaling processes and interactions with different molecules. All these processes tightly regulate the translational and post-translational processes which decide the fate of the newly synthesized polypeptide chain. Thus a particular protein may see different environments which lead to different denatured states during the course of its function. Some of the denatured states may lead to soluble aggregates, which occasionally lead to diseases [3].

When a polypeptide chain begins to fold starting from a denatured ensemble, each molecule in the ensemble can, in-principle, fold along a different path. In this scenario, the starting state in terms of the conformational preferences across the polypeptide chain will have a significant influence on the path the molecule adopts; different denaturing environments inside a cell can create different initial states for the protein to fold from. If the chain already has some structure, that may form the nucleus for additional structure to build upon, and this will reduce the search options for the solvent-exposed chain in the multi-dimensional conformational

vel details about the perturbations caused by 9.7 M urea using NMR and finally compare the urea-mediated unfolding with that using Gdn-HCl. Gdn-HCl is highly charged as compared to urea which is neutral and this is expected to have an influence on the unfolding mediated by the two denaturants; the former may lead to more collapsed state due to electrostatic screening. Our data reveal that the unfolding mechanisms by the two denaturants are indeed different. Whereas Gdn-HCl unfolding is two-state [8], urea-mediated unfolding is more complex and hence the structural and dynamics characteristics of the denatured states created by the two are different. These provide clues about the differences in the potential folding initiation sites for the folding that may follow on dilution of the denaturants. This study will form the basis for a detailed elucidation of the urea dilution driven self-association pathway of the protein, along the same lines as has been recently demonstrated in the case of self-association driven by guanidine dilution [7]. Consequently, the variability in the assembly details—high resolution picture of which is still unknown—if any, can be unraveled.

be removed for a new structure to get formed for the protein to move towards the native state. Thus the number of folding paths for a given protein would be dictated by the number and nature of structural preferences across the length of the chain.

In view of all these, it is important to understand the characteristics of the various denatured states, with regard to their topologies, heterogeneities and motional characteristics, their modulations due to changes in environmental conditions, etc. at atomic level detail. In vitro, different denatured states can be created by use of different denaturants, such as, Gdn-HCl, urea, SDS, extreme pH conditions, etc. Although these may not exactly represent the denatured states, in vivo, they help sample the ensemble quite widely and thus allow investigation of the folding processes, in general.

In this background, we present here a comparative study of the structural and dynamics characteristics of urea-denatured and Gdn-HCl-denatured states of the GTPase effector domain (GED)[9] of dynamin, a crucial protein in clathrin mediated endocytosis. GED plays important roles both in dynamin assembly around the neck of the clathrin coated vesicles, and assists the N-terminal GTPase domain in GTP hydrolysis required for dynamin function [4,5]. The recombinant form of GED has been shown to self-assemble and form large megadalton-sized oligomers in vitro [6,7] even at micro-molar concentrations. We first describe the global charac-

*Fluorescence measurements*

Bis-ANS [4,4′-Bis(1-anilinonaphthalene 8-sulfonate) Molecular Probes, OR, USA] was prepared and the concentration was determined using the extinction coefficient, $\varepsilon_{385} = 23{,}000\ cm^{-1}\ M^{-1}$. Steady-state fluorescence emission spectra were recorded with $\lambda_{exc} = 395$ nm on a Spex Fluorolog-tM3/0F spectrofluorimeter at 27 °C using a 1 cm path length cuvette with a band pass of 1.5 nm for both excitation and emission. The emission spectra were measured from 450 to 550 nm at a scan rate of 1 nm $s^{-1}$. The denaturation profiles of 10 μM protein in Tris buffer (20 mM, pH 7.4), pre-equilibrated with varying concentration of the denaturant and bis-ANS (4 μM) for 12 h, were measured by monitoring the emission at 491 nm. The data were smoothened by three-point averaging to minimize errors due to denaturant concentration adjustments and were normalized using the following equation [10]:

$$F_{app} = \frac{S_F - S_{obs}}{S_F - S_U} \quad (2)$$

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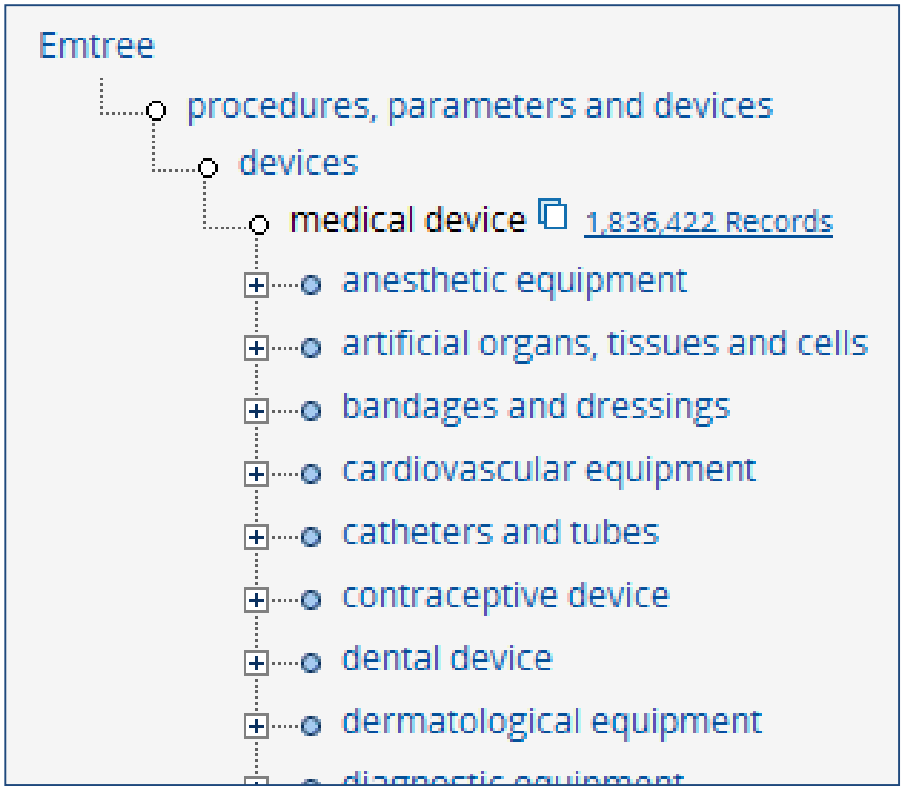
## Why is this important?

A taxonomy aided search will yield more accurate and comprehensive results. When dealing with growing amounts of information, precision is key.

## Who benefits?

Any searcher who needs a comprehensive result set: a systematic reviewer, a drug or device tracker, etc.



# So Search Results Include Articles with all Typed Terms and Synonyms

1. Emtree has > 70,000 **preferred terms** for searching *(these are the terms displayed with records),* including over 30,000 drugs
   (MEDLINE has only 27,000 terms, including ~8,500 drugs)
2. Emtree has > 290,000 **synonyms**, which can be used for searching since they **map** to the preferred terms
   (Scopus has no synonyms, so fewer terms are available for searching)
3. Emtree has an extensive **tree structure** making it possible to search on **groups** of terms
   (e.g. all monoclonal antibodies)
   (Such searches are impossible on Scopus, which has no tree hierarchy — e.g. a Scopus search on "heart attack" misses records mentioning "myocardial infarction" or articles indexed using the Emtree term "heart infarction)

**Additional information:**
Drug and disease terms are qualified by **searchable sub-headings** (e.g. drug therapy) describing their precise role in the article

**What is mapping?**
Mapping means that searchers get the **same results** regardless of which term they use, e.g. **Vioxx** (synonym) or **rofecoxib** the preferred term)

# Embase Includes Subheadings

## How is this different?

Embase has subheadings, which provide detailed drug or disease context.

## Why is this important?

Subheadings can reveal a great deal of information about the full text article, allowing for easier and better (more accurate) content filtering.

## Who benefits?

Any searcher who needs to shift through a gigantic stack of literature and needs help in drilling down to a relevant selection.