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REVIEW ARTICLE

How membrane proteins work giving autonomous traverse pathways?

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Abstract Enormous progress in computational chemistry shifted experiments toward predictive approaches. Such a paradigm shift applies to all branches of chemistry, especially to structural chemistry. To help the transfer of new knowledge in drug design practice, we reconsider a few vibrant topics of protein dynamics engaged in making *predictions* based on the timing of the events that are simulated. However, a complete explanation of the "dynamic evidence" also requires a reference to the time window allowing a prediction of the endpoint. Pioneering achievements disclosing the structure of large membrane proteins and their assemblies enabled the prediction of traverse pathways shaping membrane protein functions—essentially the efficacy of membrane proteins. Invoking significant advances made in characterizing the solute and ion symport of specific proteins through molecular dynamic simulations, early formation of a new type of solute–ion structure has been exposed as a prerequisite of Na^+ symporter function. We demonstrate that the computational chemistry is one of the most appropriate models to study traverse pathways, and we also clarify the importance of the art of fast experimental techniques.

Keywords Concept review · Membrane proteins · Traverse pathways · Transporters · Sodium and chloride symport · Scaling dynamics

Dedicated to Professor Magdolna Hargittai on the occasion of her 70th birthday.

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Introduction

Prediction of new types of inorganic structures that cannot easily be measured by experimental techniques is one of the main fields of interest of Hargittai [1–10]. In presenting Hargittai, we wish to recall Bacon first. In *The New Organon* (1620) [11], Bacon surveyed experimental paradigms revealing various forms of nature ingeniously phrasing "…the form that comes to light in a single instance leads the way to the discovery of it in all the rest….. shifting instances include not only those in which the nature under study shifts toward production or toward destruction, but also those in which the nature shifts towards increasing or decreasing. It's because these also contribute to revealing the form." Better understanding beside protein structure, the protein folding and unfolding in a crowded [12–14] milieu has been significantly advanced through the past years by different methods of protein structure determination [15–21] and by recent developments in protein modeling and molecular dynamics (MD) simulations [22–27]. Rapidly expanding data were delivered on proteins' in vivo functions, by covering topics such as conformational selection versus induced fit, agonism versus antagonism, prediction of substrate efficacy, antidepressant mechanism, or biotechnological applications of intrinsically unstable/disordered proteins [28–33].

Traverse pathways, forced intrinsic dynamics, and efficacy

Below, we aim to introduce the emergent conception of traverse pathways as autonomous elementary functions of membrane proteins, and key players of molecule and information transformation between the extra- and intracellular

space of living cells. Recurrent alteration of integral membrane proteins in water environment operated by specific perception of forces and forced intrinsic dynamics invokes the existence of cause-related autonomous *traverse* pathways from active to relaxed conformational states. Here, we intend to use the word "traverse" as the leading explanatory factor which should no doubt be the most important specification of signalling membrane proteins at work. Choosing the traverse rather than the transition conformation of the system helps to understand causality (i.e., what steps are required to reach the endpoint). Forces at work include (1) membrane- and H-bond network environment-associated mechanical forces [34, 35] and (2) water [36–39], pH [40, 41], ion [42–44], or ligand [45–51] reliant chemical as well as electric [52, 53] forces, or (3) light absorption [54].

By framing quantitative description of movement, called first into question by Zenon's "The Achilles" paradox (Fig. 1), we rephrase the contradiction as to finding the traverse pathway of a membrane protein by a Gibbs functional takes infinite time. However, membrane proteins respond within a definite time. In order to understand the uniqueness of protein function, we refer to forced intrinsic dynamics of membrane proteins based on Ben-Naim's arguments on "Levinthal's question revisited, and answered" [55] and subsequent discussions (*see* for example [56, 57]). We may also rephrase Ben-Naim's claim answering Levinthal's question "How proteins fold to give such a unique structure" into the paradox of "How membrane protein traverse from the starting to the endpoint conformations to give such a unique pathway." In addition to hydrophobic effects, local Gibbs energy minima are also shaped by hydrophilic interactions [55], which can make intrinsic dynamics of membrane proteins causal and predict the ratio (output response)/(input force), i.e., efficacy—the major enigma of drug design and discovery.

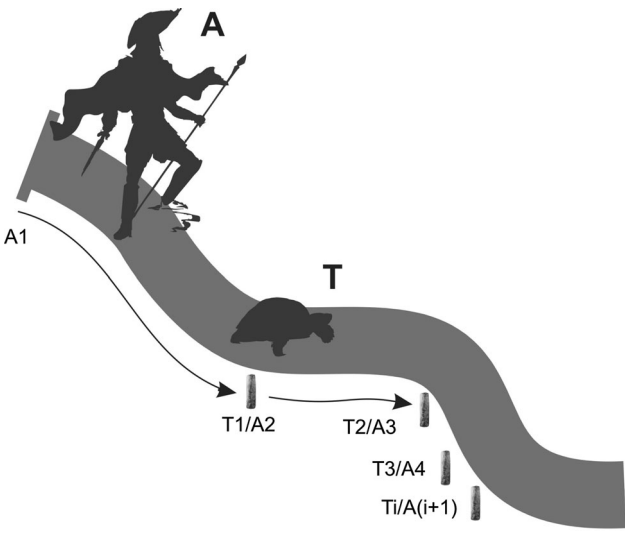

Fig. 1 Competition of forced movement cycle from states A1 through A(i + 1) and T1 through Ti. All states are represented by a conformational ensemble. Which assembly does prevail?

Membrane transporters

When taking examples of autonomous traverse pathways, we turn to membrane transporters in general and neurotransmitter sodium symporter (NSS) family in particular. This is because the information on structure and function of various types of membrane transporters, including galactose [58, 59], excitatory aspartate [60], glutamate [61–64], inhibitory γ-aminobutyric acid (GABA) [30, 65–69], dopamine [70], ATP-binding cassette [24, 71–75] transporters, and cystic fibrosis transmembrane conductance regulator (CFTR) [76–78] is promptly expanding. Taking alternate access traverse pathway of sodium and chloride ion movement-driven substrate transport as an example, we and others have shown how validated all-atom MD calculations may reveal traverse conformations of the protein–substrate complex enabling the design of more effective transporter inhibitors or activators in the future [70, 79–84].

MD simulations of NSSs subtypes, i.e., modeling interactions between the solute and the transporter protein in the presence of structurally bound sodium and chloride ions have provided a ring-like sodium-GABA structure [80] (Fig. 2). Previously being only known in vacuo, the formation of the ring-like GABA in the proteinaceous media is rather unique and draws attention to sodium ion coordinated within the substrate-binding crevice as an important factor in the formation of an intramolecular H-bond. The formation of GABA-Na^+ structure is energetically favoured, asserting an unbounded traverse conformation of the substrate [30, 66–68, 80]. This result may also be conceivable by manifesting the principle of the

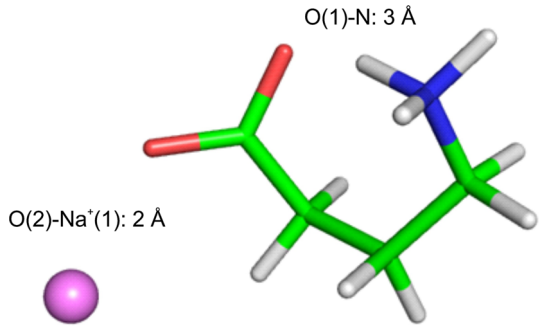

Fig. 2 Non-bonding ring-like traverse conformation of GABA in GAT1. GABA-O(2)-Na^+(1) = 2 Å, GABA-O(1)-N = 3 Å. Data correspond to the structure of sodium-complexed GABA in the homodimer of neurotransmitter sodium symporter family member GAT1 [80]

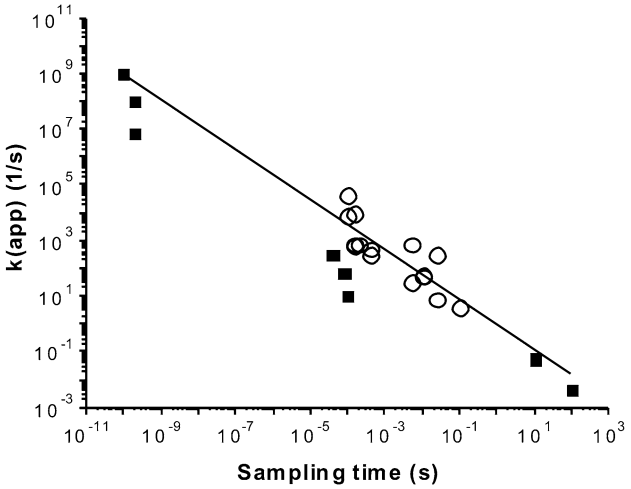

Fig. 3 Is scaling dynamics valid for membrane protein assemblies? *Open circles* and *fitted line* represent receptor channel opening [89]. *Filled squares* correspond to data for neurotransmitter sodium symporter family member GAT1 [80]

simplest mechanistic clue in the case of sodium-facilitated substrate transport. Furthermore, we can also depict events like (1) interactions between structurally bound chloride and sodium ions and (2) the appearance of intracellular water nearby the binding crevice. The latter event may anticipate the intracellular release of neurotransmitters such as GABA [80] or dopamine [85], i.e., the endpoint of traverse pathways for these transporters. This way, MD simulation shows mechanistic clues substantiating "alternate access" traverse pathways for secondary membrane transporter family members characterized by the leucine transporter (LeuT) symmetry [70]. Based on new knowledge obtained with short- and/or longer-scale simulations [27, 68, 80, 85], we may place LeuT homologue membrane transporters, which show consecutive sequence of interactions between small-molecule organic solutes and protein-bound physiological ions and water, in the context of traverse pathways driven by chemical forces. In our view, short- and longer-scale simulations [27] can be validated by data obtained from experiments employing techniques of fast chemical kinetics with widely different sampling rate (Fig. 3). Rate parameters estimated by the appearance of Na^+–substrate complex in MD simulations fit the line of transport data (Fig. 3: filled squares), suggesting that the formation of the complex is causally related to the endpoint, i.e., the inward release of the substrate. Moreover, such an association of transport data indicate that scaling (self-similar) dynamics rules a wide variety of membrane proteins regulating external information processing (Fig. 3: open circles). These re-emerging themes of stochastic versus deterministic (self-similar) protein dynamics [86–88] may recall universality of membrane protein responses as hypothesized [80, 89].

Conclusion

Understanding spatiotemporal appearance of traverse pathways shaping membrane protein functions in polarized cells remains a principal goal of chemical science and drug design practice. In the last couple of years, significant advances have been made in various solute and ion transport processes in addition to better understanding of channel gating and receptor–effector coupling. In addition, it has become evident that the binding interaction between the traversing molecule and the membrane protein produces intrinsic conformational changes due to non-covalent interactions including H-bond, charge transfer, steric repulsion, and hydration. Based on these data and facts, we took the alternate access traverse pathway of secondary transporters as an example to show how validated all-atom MD calculations may reveal traverse conformations of the substrate and thus will enable the design of more effective drugs as modulators of transport proteins (e.g., inhibitors).

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