Probing Alternating Access in Sugar Symporter vsGLT

Membrane Transport

Uniport
Symport
Antiport
Oncotransport

Solute Sodium Symporters

Use electrochemical gradient of sodium

Coupling ratio = number of sodium ions moved per substrate molecule

Examples:
- dopamine transporters (transmission of electrical signals)
- sugar transporters (lysate of sugar required for diet of all mammals)
- iodide transporters (uptake of iodide in thyroid, underexpressed in thyroid cancer patients)

Function
- Adsorption of carbohydrates in the gut
- Readsoption of sugars in the kidneys

Previous Research
- Cloned by Wright in 1987
- Structure solved by Abramson and Wright in 2008

Biomedical Significance
- Metabolism
- Oral rehydration therapy
- GGM/FGM
- Possibly diabetes

Coupling ratio of human transporter SGLT1: 1 sugar : 2 sodium
Coupling ratio of bacterial transporters: 1 sugar : 1 sodium
Reducing Structure

Go models
- Close residues
- Stabilized if a native contact
- Destabilized if not

The Weighted Ensemble Method

Homology modeling of the outward state
- No outward-facing structure for vSGLT
- Model based on LeuT
- Sequence alignment
- Structural alignment
Research Objectives

Objective 1: Analyze weighted ensemble trajectories

Objective 2: Propose a more accurate SGLT2-binding structure for SGLT2

Objective 3: Create a more accurate alternating access trajectories

Overall Research Objective:
To provide an accurate description of the alternating access pathway for the galactose transporter SGLT2

Results

Successful Trajectories

- 3 months on 8 cpus
- Generated 1154 trajectories

Distribution of Trajectory Transition Times

Three Independent Trees
Residue Distances

Kink Angles

Transmembrane Flips (rmsd):
Preliminary Findings

Future Research
- Improved code for kink angles
- Comparison of helix crossing angles
- RMSD calculations across all trajectories
- Consideration of hypotheses in literature (e.g., Forrest et al)
- Continuation of work on Mhpl (NCS1)-based model
Michael Grabe, Ph.D.
Department of Biological Sciences
Department of Computational Biology
University of Pittsburgh

Seungho Choe, Ph.D.
Department of Biological Sciences
University of Pittsburgh

Keith Callenberg
Department of Biological Sciences
University of Pittsburgh

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