crystals and to outline the frontier comes through between crystalline and quasi-crystalline local rules.

Keywords: delone set, local rules, long-range order

MS.84.4

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Aperiodic structures, order and disorder, complexity and entropy

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Artificial aperiodic structures have recently been the subject of extensive and intensive research, resulting in layered quasiregular heterostructures, as well as photonic and phononic metamaterials with possible applications such as optical and acoustic bandpassfilters or photonic waveguides. The Fourier spectrum of the Prouhet-Thue-Morse sequence is known to be singular continuous; yet its dynamical spectrum has a pure point part. This confronts us with experimental challenges to produce physical realizations of the structure in one, two and three dimensions, perform diffraction experiments and devise an experiment to reveal the dynamical spectrum.

We are interested in fundamental questions about determinism, order and "disorder" and their quantification. Specifically, we study multidimensional generalizations of the standard substitution sequences. Here we present and discuss some two-dimensional instances of the Prouhet-Thue-Morse and paperfolding systems. We compute their rectangle complexities; these are at most polynomial implying zero entropy. We also report a novel substitution method to produce multidimensional paperfolding structures. We suggest to concisely characterize the complexity by the exponent of its leading term. We point out that the perfectly deterministic Champernowne and Copeland-Erdős sequences have entropy ln2 exactly like fair Bernoulli. These examples clearly show that entropy, regardless of its definition, does not distinguish between deterministic and random systems. There still remain many unanswered questions.

Keywords: aperiodic, complexity, entropy

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Inhibition of SNARE-mediated membrane fusion by VARP

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SNAREs are the small, mainly Type II membrane proteins that provide much of the mechanical energy and specificity to vesicle: organelle and organelle:organelle fusion events. Defined combinations of 3 Q-SNAREs from one membrane and 1 R-SNARE from another interact highly specifically and selectively to form *trans*-SNARE complexes through their SNARE motifs. Such SNARE-mediated membrane fusion processes must be tightly regulated. Members of the n-Sec1/Munc18 family regulate the incorporation of Q-SNAREs into SNARE complexes. We have identified the multidomain, endosomal rab32/38 effector VARP as the first example of an R-SNARE-binding regulator of SNARE complex formation. We demonstrate that VARP co-localises with and binds to the key R-SNARE of the late endocytic pathway, VAMP7. This crucial R-SNARE is highly conserved across species, ubiquitously expressed and is involved in many membrane traffic pathways, especially in fusion events between lysosomes and other cellular membranes including endosomes and the cell's limiting membrane. We have determined the structure of the Ankyrin repeat domain of VARP in complex with the cytoplasmic portion of VAMP7. VAMP7 is bound with its N-terminal longin domain bound back onto its SNARE motif. This closed conformation of VAMP7 is stabilized by intramolecular interactions between the SNARE motif and the longin domain as well as intermolecular interactions between the two parts of VAMP7 and the Ankyrin stack of VARP. We show that the trapping of VAMP7 in this inactive conformation by VARP inhibits the ability of VAMP7 to form SNARE complexes since the SNARE motif binding back onto the longin domain is mutually exclusive with the participation of the SNARE motif in SNARE complex formation. The mode of binding of VAMP7 to VARP contrasts with that of VAMP7 bound to the endocytic trafficking coat protein Hrb. In this latter case, it is the open conformation of VAMP7 that interacts with Hrb, which is formed when VAMP7 participates in SNARE complex formation. VARP is therefore a new and important regulatory component of the membrane fusion machinery of the endocytic pathway, which can control the fusion of VAMP7-mediated late endocytic compartments containing hydrolytic enzymes with other membranes.

Keywords: cell biology, SNARE-mediated membrane fusion, regulation

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Structure of the human histamine H1 receptor with doxepin

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Histamine H1 receptor (H1R) is expressed in various tissues and involved in allergic responses. The antihistamines generally act as inverse agonists for H1R and alleviate the symptoms of allergic reactions. However, the first-generation antihistamines are known to show considerable side effects such as sedation and dry mouth, because of penetration across the blood-brain barrier (BBB) and low receptor selectivity. Second-generation antihistamines are less sedating and have fewer side effects. The improved pharmacology of the second-generation zwitterionic drugs can be attributed to a new carboxylic moiety, in combination with the protonated-amine, which reduces brain permeability and improves the H1R selectivity. However, certain second-generation drugs still show cardiotoxicity because of the interaction with cardiac potassium channels.

Using *in meso* crystallization technique, we succeeded to determine the structure of H1R overexpressed in *Pichia pastoris*. For overexpression, we replaced most of the third cytoplasmic loop with T4-

lysozyme and truncated the N-terminal 19 residues. The structure was determined at the 3.1 Å resolution with a first-generation antihistamine, doxepin. The structure allows us to characterize its ligand-binding pocket in detail. Doxepin sits much deeper in the pocket than the antagonists in other aminergenic G protein coupled receptor (GPCR) structures and directly interacts with the highly conserved Trp428, a key residue in GPCR activation. Asp107, a strictly conserved residue in aminergic receptors, forms an anchor salt bridge with the amine moiety of doxepin. The antihistamine is also surrounded by highly conserved residues among aminergenic receptors including Ile115, Phe424 and Phe432. The well-conserved pocket and its mostly hydrophobic nature contribute to low selectivity of doxepin and other first-generation compounds causing considerable side effects. The pocket is associated with an anion-binding region occupied by a phosphate molecule.

Docking of various second-generation antihistamines reveals that the unique carboxyl-group present in this class of compounds interacts with Lys191 and/or Lys179, both of which form part of the anion-binding region and are not conserved in other aminergenic receptors.

The structural details of the antihistamine-binding pocket of H1R will be highly beneficial for guiding rational design of new antihistamines that do not penetrate the BBB while maintaining H1R selectivity.

Keywords: histamine, receptor, structure

MS.85.3

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Towards a structural understanding of drug and peptide transport within the proton dependent oligopeptide transporter (POT) family

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The proton dependent oligopeptide transporters (POTs) are a large family of integral membrane proteins that use the inwardly directed proton electrochemical gradient to transport small peptides, amino acids and nitrate across cellular membranes in both pro- and eukaryotic cells. Evolutionarily the POT family sits within the much larger Major Facilitator Superfamily (MFS), members of which contain a common structural motif of 12 transmembrane-spanning alpha-helical segments. The human genome contains four members of this family, two of which, PepT1 and PepT2 are responsible for the absorption of dietary peptides in the small intestine and peptide re-absorption in the kidney. Peptide transporters also contribute significantly to the oral bioavailability and pharmacokinetic properties of a number of important drug families, such as the beta-lactam antibiotics. To gain further insight into the molecular mechanism of drug and peptide transport, we determined the crystal structure of a prokaryotic member of the POT family, $PepT_{So}$, with similar substrate specificity and a high degree of sequence conservation to the mammalian PepT proteins [1]. The structure of $PepT_{So}$, together with our associated kinetic data, provides valuable new insights into mammalian peptide transport and provides the starting point for further structural and biochemical studies on this pharmaceutically important transporter family.

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Keywords: major facilitator superfamily, occluded state, peptide transport

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Molecular basis of substrate-induced permeation by an amino acid antiporter

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Transporters of the amino acid, polyamine and organocation (APC) superfamily play essential roles in cell redox balance, cancer and aminoacidurias. The bacterial L-arginine/agmatine antiporter, AdiC, is the main APC structural paradigm and shares the "5+5 inverted repeat" fold found in other families like the Na+-coupled neurotransmitter transporters. The available AdiC crystal structures capture two states of its transport cycle [1-3]: the open-to-out apo and the outward-facing Arg+-bound occluded. However, the role of Arg+ during the transition between these two states remains unknown. Here, we show the crystal structure at 3.0 Å resolution of an Arg+-bound AdiC mutant (N101A) in the open-to-out conformation, completing the picture of the major conformational states during the transport cycle of the "5+5 inverted repeat" fold-transporters [4]. The N101A structure is an intermediate state between the previous known AdiC conformations. The Arg+-guanidinium group in the current structure presents high mobility and delocalization, hampering substrate occlusion and resulting in a low translocation rate. Further analysis supports that proper coordination of this group with residues Asn101 and Trp293 is required to transit to the occluded state, providing the first clues on the molecular mechanism of substrate-induced fit in a "5+5 inverted repeat" fold-transporter. The pseudo-symmetry found between repeats in AdiC, and in all fold-related transporters, restraints the conformational changes, in particular the transmembrane helices rearrangements, which occur during the transport cycle. In AdiC these movements take place away from the dimer interface, explaining the independent functioning of each subunit.

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Key words: AdiC, APC transporter, 5+5 inverted repeat fold

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Crystal structure of the copper pump

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