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

Acta Cryst. (2011) A**67,** C185

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

MS.85.1

Acta Cryst. (2011) A**67,** C185

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

MS.85.2

Acta Cryst. (2011) A**67,** C185-C186

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-