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Artificial Water Channels: Inspiration, Progress, and Challenges

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Introduction

The Faraday Discussion on Artificial Water Channels held in Glasgow, UK in June 2018 provided an exceptional and timely opportunity for researchers of diverse backgrounds including, but not limited to, structural biology, biomimetic chemistry, polymer chemistry, supramolecular chemistry, computer modelling, and engineering to share their ideas and results on a topic of both fundamental and practical importance, and to envision the future of this rapidly expanding field. The organizing committee should be congratulated for doing a fantastic job in arranging an outstanding program and all the attendees for contributing to this enjoyable and highly stimulating meeting. It was a great honour to deliver the concluding lecture at the meeting. The highly interdisciplinary nature of this meeting makes summarize its scientific content a daunting task. Instead of amassing all the exciting ideas, main themes, discussions, and conclusions, this summary tries to outlines the spirit of this wonderful meeting based on the tradition of the Faraday Discussions by presenting this paper in partially improvised way from a more or less personal perspective.

Inspiration from Nature: Size does matter

Among the many sophisticated and complex biological machineries found in nature, membrane channels are proteins that are responsible for transporting materials, i.e., ions and molecules, in and out of the cell.[1] For example, potassium ion and water channels represent two classes of the best studied membranes channels with astoundingly high specificity and permeability. Potassium channels, found in all living organisms, facilitate the transmembrane passage of K^+ ions at a rate near the diffusion limit while showing superb ion selectivity by rejecting other ions including Na^+.[2] For water transport, Nature offers a fascinating class of integral membrane proteins called aquaporins (AQPs) that mainly facilitate water to cross the cell membrane with water flux that is orders of magnitudes faster than for other classes of transporter proteins, while not allowing other ions including protons, to pass.[3] Architecturally, AQPs form homotetramers in the cell membrane, with each of the four monomer being a water channel. The aqueous pathway of an AQP has the shape of an hourglass that consists of two vestibules connected by a narrow pore of ~20-30 Å long and 3-4 Å across. In this narrow pore, two conserved segments are responsible for selectivity: the NPA-signature motifs in the centre of the channel and the selectivity filter (SF), or aromatic arginine (ar/R) region, on the extracellular side, 8 Å above the NPA-signature motifs (Fig. 1). Due to its positive charge, the selectivity filter strongly rejects charged molecules or ions, including protons. The unique distribution of amino acid residues along the pore wall of a water specific AQP (e.g., AQP1) provides an amphiphilic environment that allows water molecules to readily get in but keeps them from binding too

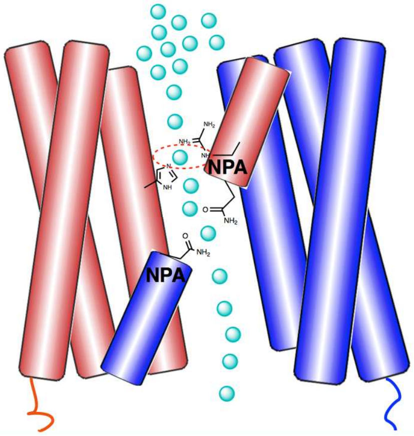

Fig. 1 The two conserved segments of aquaporins: the NPA-signature motif and the selectivity filter (SF, indicated with red dashed circle) above the NPA motif on the extracellular side of the channel. These two elements guide single-file water molecules

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(cyan circles) through a narrow pore, where selectivity for water is conferred by electrostatic and steric factors.

tightly, which account for the nearly free flow of only water molecules in and out of the cell through the AQP channel. Water molecules are oriented by these two segments through the narrow pore in which selectivity for water is realized by electrostatic and steric factors.

In spite of their distinctly different functions, highly selective biological channels like AQPs and the potassium channels share common architectural features including narrow pores running midway through the membrane, which confines the ions or water molecules being transported into single files; and selectivity filters responsible for the extraordinary mass-transporting selectivity that has not been duplicated by any artificial system. In fact, the structural and functional sophistications, along with the transport rates, shown by channel proteins remain the “holy grail” of molecular and ion transport.

Recent investigations of biological pores: (The lack of) hydrogen bonding sites also matters

Invaluable new insights into single-file water transport through narrow biological pores of a few angstroms wide are provided by Peter Pohl in his introductory lecture of this meeting.[4] Based on a study involving both theoretical consideration and experimental verification, the factors influencing single-file translocation of water through such channels were meticulously examined. It is concluded that, in addition to the sub-nm size of a channel, the number of hydrogen-bond donating or accepting residues on the channel wall is the other major determinant of single-file water flow across biological channels, while dehydration penalty at the channel mouth[37] and conformational transitions of water channels are the other two less important factors. Based on these conclusions, it was reasoned that the water permeability value (ρ_f) of carbon nanotubes obtained *in silico*,[5] which tops that of GlpF, the highest among the biological channels examined, is likely due to the inability of water molecules to form any hydrogen bonds within the CNT pore.

The discrepancies between predictions made by MD simulation and reasoning based on thermodynamics, i.e., nanopores of 8.1 Å across could conduct water in single-file, while rejecting hydrated sodium and chloride ions, and a recently published experimental study by Noy et al.[6] showing the transport water, K^+ and Cl^- through a 10-nm long carbon nanotube with a 6.8 Å diameter, were discussed. The corresponding discussions and debate are apparently beneficial to the field by stimulating further thinking and offering new insights to this very important topic.

Besides, Susanna Törnoth-Horsefield talked about the importance of full length regulatory proteins on AQP regulation;[7] Paul Vasos presented a potentially very useful NMR method that may be used to monitor transmembrane water transport in real time;[8] and Mark Sansom discussed results from simulations on water and hydrophobic gating based on protein ion channels.[9]

Non-biological channels: Feedback from CNT pores, graphene pores and graphene oxide channels

Extraordinary mass-transport behaviour had also been revealed with non-biological nanopores. In 2001, Hummer *et al*.[10] reported their results from molecular dynamics (MD) simulations performed on the 8.1-Å pore of a single-walled carbon nanotube (CNT). Water molecules were found to spontaneously and continuously fill and rapidly pass through the highly hydrophobic sub-nm CNT pore. Such a counterintuitive observation suggested that CNT pores, with their rigid, non-deformable, and hydrophobic structures, might serve as unique molecular channels. This prediction was experimentally examined in 2006 by Holt *et al.*,[11] who showed that the transport of water and methane through aligned CNTs with ≤2-nm pores had spectacular fluxes that were several orders of magnitude faster than classical theories had predicted. In addition to unusual water transport, other MD simulations also showed that, reducing pore size to the sub-nm range results in drastically enhanced mass transport and surprising ion selectivity. Carrillo-Tripp *et al.* reported that sub-nm pores with diameters smaller than 13 Å selected K^+ over Na^+.[12] Shao *et al*. compared the hydration of K^+ and Na^+ in single-walled CNTs and showed that constraining a hydrated K^+ inside narrow CNTs with diameters of 0.60 and 0.73 nm was more favourable, while the situation was reversed inside wider CNTs with diameters of 0.87, 1.0, and 1.28 nm.[13] MD simulations done by Cohen-Tanugi and Grossman [14] showed that graphene with sub-nm pores could surpass the water permeability of polymeric reverse osmosis membranes by 2 to 3 orders of magnitude while rejecting most ions.

Within this meeting, Gerhard Hummer described recent work on MD simulations of CNT porins in lipid bilayers, which shows an increased lipid order around the CNTs;[15] Aleksandr Noy discussed the influence of PEG additives and pore rim functionalization on water transport through sub-nm CNT pores.[16]

Anomalous mass transporting behaviours are not limited to “conventional” nanopores such as biological or CNT channels. For example, 2-nm-deep hydrophilic channels fabricated on silica also showed great enhancement of mass transport.[17]

The emergence of two-dimensional (2D) materials, especially those based on graphene, allows the fabrication of conceptually novel nanochannels. For example, stacking graphene oxide (GO) sheets together affords 2D channels that are connected by slits between the edges of neighbouring sheets or pores with the GO planes.[18] In the stacked GO sheets, water molecules first diffuse into the surface through-plane gaps, then transport along the interlayer nanochannels. Varying the spacing between adjacent GO layers would afford 2D nanochannels with sub-nm interlayer spacings that are comparable to the size of water molecules, resulting in confined transport of water molecules. Such sub-nm 2D channels are expected to exhibit very high water flux while rejecting most other species,[19–21] with great promise in applications such as water desalination, gas separation, and solvent drhydration.[11,22] However, reducing interlayer spacing to the sub-nm range and maintaining such spacing against the swelling of GO layers in aqueous solution present major challenges that are being addressed. For example, a work recently published by Fang *et al*. realized the control of interlayer spacing between GO layers to angstrom precision using cations.[23] An 11.4-Å spacing was obtained with KCl while other cations with larger hydration radii gave wider spacings. Membrane controlled by one type of cation showed efficient and effective exclusion of other cations having larger hydration shells.

In this meeting, Baoxia Mi discussed results from a study on comparing the interlayer spacings of pristine, reduced and covalently crosslinked GO sheets using an online monitoring system based on an integrated quartz crystal mass balance (QCM-D) and ellipsometry.[24] Results from this study demonstrate that covalent crosslinking, based on reaction between ethylenediamine and the epoxide sites of GO, is effective in preventing the GO layers from swelling by maintaining the interlayer spacing. The mass transport within 2D graphene and GO channels were compared with MD simulations, which revealed that water flux through the graphene channels is almost two orders of magnitude higher than GO channels. This difference is attributed to the presence of oxygenated functional groups on the GO plane that impedes water movement. Findings made by this study indicate the important factors, such as non-swellness, precisely controlled interlayer spacings, and smooth channel walls, that need to be considered in the design and fabrication of next-generation 2D channels.

Synthetic channels: Building nanopores from scratch

Efforts to create synthetic channels started three decades ago[25] and are ongoing, with the majority of systems being on ion transport[26] and very few on molecular transport.[27] Known examples of synthetic channels include both self-assembling and unimolecular ones. Some of the earliest artificial channels are unimolecular or bimolecular with membrane-spanning lengths (Fig. 2). Such channels were constructed by attaching either linear chains, such as the first artificial ion channel reported by Tabushi *et al*.,[25] or those based on crown ethers exemplified by systems developed by Fyles,[28] Gokel,[29] Lehn,[30] Matile,[31] and Voyer,[32] to macrocyclic scaffolds derived from cyclodextrins and calixarenes, or rod-like structures such as α-helices or *p*-octiphenyls, or by simply connecting crown ethers with flexible aliphatic linkers. Ion transport had been demonstrated with numerous examples. However, these early artificial ion channels do not contain defined, tunable pore size due to the flexibility of the attached linear chains, crown ethers, or the overall structures.

Unimolecular channels with defined sub-nm pores are rare but encouraging examples have appeared in recent years. Along the line of modifying macrocyclic frameworks with linear "tails", Hou *et al*.[33] developed an elegant system by appending pillarenes with linear, semi-rigid chains that align along the long axes of the resultant tube-like structures. The introduced chains are based on oligopeptides and oligohydrazides capable of engaging in additional H-bonding interactions that reduce the flexibility of tube-like structures. Such tubular molecular structures were found to readily partition into the lipid bilayer and effectively transport ion and molecules including water. In this meeting, Junli Hou described recent effort and encouraging results made by his group on developing membrane-bound antibiotics based this series of tubular-like structures they developed.[34]

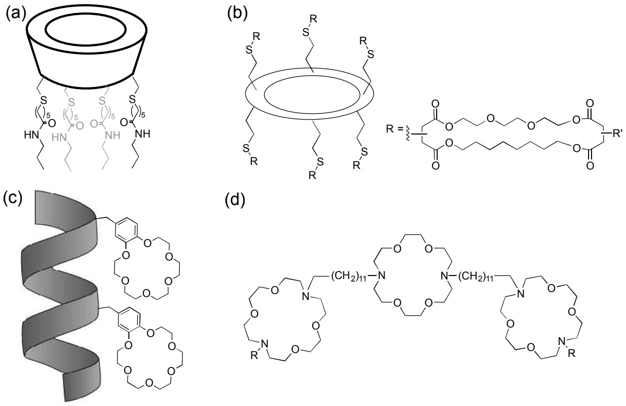

Fig. 2 A few examples of early synthetic ion channels reported by: (a) Tabushi,[25] (b) Fyles,[28] (c) Voyer,[32] and (d) Gokel.[29]

A more recent example of unimolecular pores was reported by Dong *et al*.[35] based on polymers with a rigid aromatic backbone that adopts a helical conformation containing inner pores of a defined size. Polymer chains with narrow molecular weight distribution and the length that allows the helices to span the lipid bilayer were separated by fractionation and found to serves as effective transmembrane channels. Further development of this system, for example, by developing synthetic method for preparing monodisperse oligomers with the same backbone, should afford unimolecular channels with completely controlled and tunable lengths.

In addition to unimolecular or bimolecular channels, self-assembling synthetic channels consisting of multiple identical molecular components have also been developed. Some of the earliest examples include the "minimalist" channels reported by DeGrado *et al*. in 1997 based on bundles of amphiphilic α-helices,[36] and peptide nanotubes formed by stacked cyclic peptides composed of alternating D- and L-α-amino acids reported in 1992 by the group of Ghadiri.[37] Another fascinating systems of self-assembling channels were created by the group of Matile,[38] based on artificial β-barrels formed from the self-assembly of rod-like *p*-oligophenyls modified with short peptide chains. These rigid-rod β-barrels offer large multi-functional pores that served as ion and molecular channels, hosts for molecular recognition, sensors, and catalysts.

In early 2006, the Davis group published their work on developing G-quartet ion channel.[39] The cyclic G-quartets undergo π-stacking into columnar assemblies that were stabilized by covalent capture based on olefin metathesis performed on within lipid bilayer. This elegant strategy transforms a self-assembling channel with modest stability into a robust unimolecular one that was active in transporting Na^+. In this meeting, Jeffrey Davis presented recent work from his group on extending their G-quartet-based system into developing hydrogels.[40]

In 2008, we reported self-assembling transmembrane ion channels based on a series of aromatic oligoamide macrocycles that have a persistent shape and a non-deformable, hydrophilic cavity of ~8.5 Å across.[41] The self-assembling channels, with their non-collapsible, hydrophilic inner pore defined by the rigid macrocyclic molecular components, were found to by highly conducting, with conductance comparable to that of large protein pores such as that of α-hemolysin. Results from this work have demonstrated the importance of a defined, non-deformable pore in facilitating ion transport.

In this meeting, Kazushi Kinbara talked about channels formed by designed triblock amphiphilic molecules that mimic transmembrane proteins,[42] based on a unique system his group first reported in 2012.[43]

Artificial water channels: Currently known systems

In comparison to the numerous artificial ion channels known today, only a handful of artificial water channels have been reported so far, due most likely to the difficulty in detecting selective water transport in artificial systems. Studies based on MD simulations predicted extraordinary water transport through CNTs,[10] especially sub-nm CNTs, years before experimental evidence supporting such predictions was available based on arrays of CNTs.[11] Discrete water channels based on CNTs did not become known until recently. Noy *et al*. reported "CNT porins", i.e., CNTs embedded in lipid membrane matrix, that facilitate water transport, presumably as single-file chains, across lipid bilayers, with water permeability exceeding that of AQPs and wider CNT pores.[6] The CNT porins still conduct ions such as K^+ and, most likely H^+ as well, with a noticeable preference for K^+ over Cl^-.

Percec *et al*. in 2004 reported helical hydrophobic pores of 14.5 Å across, based on the self-assembly of a dendritic dipeptide, and found water and proton transport through the hydrophobic pores while other cations and anions were rejected.[44]

The Barboiu group reported in 2011 the creation of an elegant system of self-assembling water channels based on imidazole (I) quartets that are stabilized by inner dipolar water wires (Fig. 3a).[45] The I-quartets, being stable in solution, the solid state, and within bilayers, form tubular channel-type chiral superstructures with confined water wires in which the water molecules are H-bonded in a way similar to those in AQP channels, suggesting that water molecules and protons can permeate the bilayer membranes through I-quartet channels. Such an expectation was confirmed with a simple molecule composed of histamine and a hexyl chain connected via a urea linkage. In lipid bilayer, the presence of this molecule resulted in high transmembrane water flux and spectacular ion rejection that was attributed to the small (<3Å) diameter of the I-quartet pore. In this meeting, Legrand and Barboiu discussed the effects of structural factors on water permeability of this series of artificial water channels, with several useful conclusions that will benefit the development of more efficient water channels.[46]

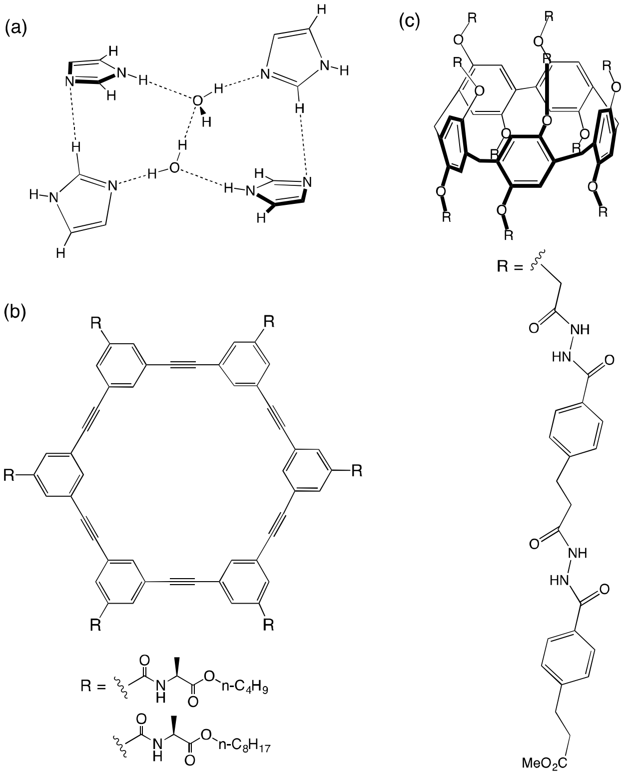

Fig. 3. Molecular and supramolecular structures for three known system of synthetic water channels reported by: (a) Barboiu,[45] (b) Gong,[47] and (c) Hou.[33]

In 2012, we reported self-assembling channels built from shape-persistent *m*-oligophenylethynyl (OPE) macrocycles that stack into helical tubes (Fig. 3b).[47] The helical stacks of the OPE macrocycles are encased in multi-fold H-bonding networks and further stabilized by aromatic stacking between the macrocyclic backbones. The resultant helical tubes, which contain a non-deformable hydrophobic inner pore of ~8.3 Å across, were found to serve as "reluctant" transmembrane K^+ channels with a small (5.8 pS) conductance only at high (3 M) concentration of KCl. Interestingly, the same transmembrane pores do not conduct Na^+ but show a strong preference for H^+ transport, suggesting the presence of H-bonded chains of water inside the sub-nm hydrophobic pore. Examining water transport through the self-assembling hydrophobic pores based on stopped-flow assays revealed a water permeability value that was estimated to be ~20% of AQP1. Our synthetically modifiable system shows that, like biological channels, without the atomically smooth inner walls of CNTs, other sub-nm hydrophobic pores can also transport water efficiently.

A beautiful artificial system that provides single- or bimolecular molecular water channels was reported by the Hou group in 2012 (Fig. 3c).[33] Pillar[5]arene derivatives with attached oligohydrazide chains that intramolecularly H-bonded to one another form tube-like structures that are stably embedded in bilayer membrane. The longest derivative has a length of 3.5 nm that matches the thickness of the bilayer and was found to efficiently transport water and HO^- ions based on single-molecular transport mechanism. This unimolecular channel, like AQPs, does not transport protons although a number of other cations can still pass. The rejection of protons by the pillar[5]arene channels is attributed to the alternative hydrophobic/hydrophilic regions in the inner pore of this molecular tubes, which disrupt the formation of water wires and thus block the proton flux, while still allowing water molecules to pass.

In this meeting, Samuel Murail presented results from MD simulations on I4 channels;[48] Rob Coalson reported results from MD simulations on water and ion transport through narrow artificial pores;[49] and Manash Borthakur discussed MD simulations on separating water and ethanol with CNTs in grapheme membranes under electric field.[50]

Fabrication of membranes: Time to get real

Membranes incorporating biological or artificial water channels as additives hold great promise in developing alternative low-energy separation technologies for water desalination, waste water treatment, and water purification.[51] Academic and industrial research efforts have been made in recent years in incorporating water channels into lipid or polymer-based matrices, with encouraging progress made toward producing practically useful membrane materials.[52] For example, aquaporins, with their nearly exclusive selectivity and ultrahigh permeability for water molecules, have attracted intense interest in serving as bio-additives for fabricating membranes that can be used for the treatment and purification of water. The corresponding technologies are expected to be considerably more energy- and cost-efficient in comparison to current ones. In this meeting, Claus Hélix-Nielsen presented their recent progress in large-scale manufacturing and purification of AqpZ expressed with E. coli.[53]

Challenges to be addressed in the use of AQPs in membranes include the development of an effective strategy to stabilize AQPs, the fabrication of robust membranes that are compatible to AQPs and keep the incorporated AQPs functional at a wide range of temperatures. Besides, the success of AQP-based large-area membranes relies on the production of large quantities of APQs at low cost.

The limitations of biological channels may be overcome by adopting artificial water channels such as those based on carbon nanotubes[54] and synthetic channels. Compared to biological and CNT channels, synthetic pores offer better synthetic modifiability and scalability and also allow controlling the physical dimensions including length and diameter, alignment, and performance of the channels. However, only several systems of synthetic water channels, including helical pore of self-assembled dendritic dipeptides reported by Percec,[43] peptide-appended pillar[5]arene channels by Hou,[33] I-quartet pores by Barboiu,[45] *m*-phenylene ethylene nanotubes by Gong,[47] and water-transporting oligoamide foldamers by Zeng,[55] are currently known.

Kumar *et al*. reported the incorporation of peptide-appended pillar[5]arenes, based on the system developed by the Hou group, into biomimetic membranes composed of lipids, in which the modified pillar[5]arene channels self-assemble into 2D arrays, resulting in membranes with a very high pore density.[56] This work represents the first attempt in incorporating synthetic organic water channels into biomimetic membranes.

In this meeting, Woochul Song and Manish Kumar discussed two selectivity trends of multi-layered pillar[5]arene membranes that showed significantly improved water permeability over commercial membranes;[57] Robert Hickey and Monish Kumar presented results on the creation of supporting layers for biomimetic membranes that incorporate synthetic channels based on crosslinked lamellar block copolymers.[58] The created membranes mimic layers of natural lipid bilayers, and have superior mechanical strength suitable for practical applications. In addition, Suzana Nunes described block copolymer films with a high density of carboxyl-modified nanopores of well controlled size (~1.5 nm);[59] Viatcheslav Freger analysed factors that are related to the enhancement and control of selectivity and salt rejection based on what are from polymeric membranes and CNTs.[60]

Conclusions: A lot more to do

Studies on biological channels over the last two decades have revealed the structural details behind the extraordinary performance of these biological machineries on material transport.[1-3] Highly selective channels such as potassium and water (AQP) channels show a common feature, i.e., the presence of a narrow pathway decorated with additional “check points” that provided both confinement and screening for the molecular and ionic species. For water transport, the paramount importance of a sub-nm pore, preferably amphiphilic as shown by AQPs,[3,61] is also shown by CNT pores,[6,10,11] graphene[62,63] and graphene oxide[18-21] channels, and more recently by synthetic molecular and self-assembling channels.[64] Fabricating biomimetic membranes with water channels offers a very promising approach for developing the next-generation separation technologies. In comparison to AQPs which have been extensively examined,[3,61] the creation of artificial water channels, especially synthetic ones that are amenable to ready structural and functional modification and can be incorporated into various 2D matrices, is still in its infancy, with much more to explore. Remaining challenges facing synthetic water channels include the precise control of pore length and the reduction of diameter down to the sub-nm range; uniform or site-specific functionalization of channel wall; homeotropic alignment of water-transporting pores; and the fabrication of membranes with molecular-thickness and with ultra-high pore densities from functional sub-nm pores. While reaching the sub-nm regime from top to bottom is becoming increasingly challenging, building structures from bottom up based on chemical synthesis offers plenty of room to work with. For example, great progress has been made in recent years on constructing shape-persistent, void-containing macrocycles and folding oligomers.[65] These structures include rigid macrocycles with non-deformable, tunable inner cavities from sub-nm to a few nm, and "hollow helices" with sub-nm pores and lengths that match the thickness of the lipid bilayer. Examining mass transport through self-assembling or molecular channels based on these organic nanopores have yielded fascinating initial results,[66] suggesting that artificial ion and water channels with properties rivalling those only observed with biological channels will no longer be a fantasy. Indeed, "There's plenty of room at the bottom"[67] for scientists to play with for years to come.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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