Recent scientific biography

My laboratory investigates several related areas: retinal circuitry, small signal transmission, self-assembly of molecular cages, virus structure and the geometry of polyhedra.

1. **Retinal circuitry:** Motivated by an interest in mechanisms of color vision and remarkable synapses in the retina, in the early '90s I began a project involving reconstruction from serial electron micrographs of the central retina of macaque monkey. I sought to identify different types of retinal cells and how they form circuits, typically from rods and the three (Long, Medium, and Short-wavelength-sensitive) types of cone photoreceptors to bipolar cells and thence to ganglion cells. We discovered a new type of S-cone driven bipolar cell that may contribute to the blueness but not the redness of short wavelength (violet) light (Klug et al., 2003). We detailed the connectivity of another S-cone driven bipolar cell that appears to contribute to both (Herr et al., 2003, Schein et al., 2004). We discovered the first morphological difference between L- and M-cones, a difference related to the number of synapses they make with one particular type of bipolar cell (Schein et al. 2011). We discovered a new type of retinal synapse (Herr et al., 2011). We showed how Müller cells (the major retinal glial cell) isolate synaptic terminals of cones and prevent undesirable crossing of glutamate from one cone's postsynaptic targets to neighboring cones' targets (Burris et al., 2002).

We also studied the output end – the synaptic terminal – of rod photoreceptors (Migdale et al., 2003), cone photoreceptors (in preparation), and bipolar cells (in preparation), all of which release glutamate neurotransmitter at active zones related to 'synaptic ribbons'. We discovered that macaque and human rod terminals have exactly two active zones (Migdale et al., 2003) and overturned the "tetrad" picture of how each ribbon was related to postsynaptic sites. By contrast, a cone terminal has ~20 synaptic ribbons, but they supply glutamate neurotransmitter to several hundred postsynaptic sites, none of which are directly opposite the release sites. We invented a "diffusion surface" at the base of the terminal to explain how glutamate could be delivered effectively to all of these sites (shown in Klug et al., 2003, Schein et al., 2011, Herr et al., 2011, in preparation). The synaptic terminal of a bipolar cell also has a fairly large number of synaptic ribbons. We discovered that the postsynaptic sites on ganglion cells are of three morphological types (in preparation).

2. **Small signal transmission:** Psychophysical experiments show that we can detect exceedingly weak visual and auditory stimuli. Indeed, when dark-adapted we can detect light when each of only a few rods absorbs just one photon. The physiological basis for such extraordinarily sensitive performance is not well understood. It is known that absorption of a single photon by a rod causes its membrane potential to change by about one millivolt, a very small amount. We argued that this change should cause the rod's synaptic terminal to reduce its rate of release of packets of (glutamate) neurotransmitter, but also by a small amount (Schein & Ahmad, 2005). The target of these packets, the rod bipolar dendrite, thus counts a small number of packets of neurotransmitter in the dark (e.g., 10) and only slightly fewer in the light (e.g., 8). But, assuming that packets are released at random intervals, the counts would have highly overlapping distributions, e.g., $10 \pm \sqrt{10}$ versus $8 \pm \sqrt{8}$.

We therefore suggested that release occurs at regular – not random – intervals and compared in detail the theoretical detection capabilities conferred by regular *vs.* random release (Schein & Ahmad 2005, 2006). We concluded that regular release allows the sort of sensitivity actually observed, whereas random release does not. We went on to evaluate the physiological mechanisms that could be used downstream

of the release process to respond differentially to strings of regular release events with intervals longer in the light than in the dark (in preparation).

We ask related questions about cone photoreceptors, which must transmit many levels of contrast, about hair cells in the auditory, vestibular, and lateral line systems, and about electroreceptors, all having to use small numbers of packets to transmit signals that are even smaller than the one millivolt in the rod (in preparation). We believe that the same principles that we have discussed with respect to synaptic signaling mechanisms in the visual system apply in the auditory system and may also apply to the formation and decoding of regular spike trains in a variety of the brain's computational modules.

3. **Self-assembly of molecular cages:** Release of packets of neurotransmitter involves fusion of synaptic vesicles with the presynaptic membrane of the synaptic terminal. To avoid enlargement of the presynaptic membrane and gross distortion of the structure of the synapse, these patches of membrane must be retrieved. Retrieval is powered by self-assembly of many copies of a protein called clathrin (MW 710,000) that sticks to the inner surface of the membrane and buds inward as it assembles into a cage that encloses the patch in the form of a vesicle. We see many clathrin-coated vesicles in the presynaptic terminals of rods and cones. Although we became interested in clathrin because of its role in endocytosis in presynaptic terminals, it has a more critical role in all eukaryotic life – budding of vesicles from one leaflet in the Golgi apparatus for fusion with another leaflet or delivery to other intracellular targets.

Clathrin can self assemble into diverse cages, all with 'fullerene' structure, related to soccer balls. Like a soccer ball, these clathrin cages have 3valent vertices and faces that are pentagons and hexagons. Carbon atoms also assemble into fullerenes, the most famous being the truncated icosahedron (or soccer ball), the new allotrope of carbon that was discovered in 1985 and named Buckminsterfullerene. Like clathrin, whose trimers act as trivalent vertices with arms, carbon atoms act as vertices with arms (bonds).

I became interested in figuring out the paths of assembly of both clathrin protein and carbon atoms and why they assemble only certain of the infinite number of mathematically possible fullerenes. We proposed the 'head-to-tail exclusion Rule' that specifies which fullerene cages can self-assemble (Schein & Sands-Kidner, 2008). Using molecular toys, computational chemistry, and an appreciation of geometry in 3D, we established the physical basis for the head-to-tail exclusion Rule (Schein et al., 2008).

By identification of recently reported clathrin cage structures, we obtained experimental confirmation of the head-to-tail exclusion Rule for small cages ($\leq$60 vertices) assembled by clathrin (Schein, 2009).

Carbon cages form a special subset of larger cages ($\geq$60 vertices) that have no adjacent pentagons, thus the Isolated Pentagon Rule (IPR). By proving that the head-to-tail exclusion Rule permits only IPR cages (Schein and Friedrich, 2008), we not only confirmed the head-to-tail exclusion Rule for carbon, but we also explained why carbon assembles only IPR cages, a mystery at the very heart of carbon fullerenes and nanotubes.

COP-II is another protein that self-assembles into cages. Its job is as critical to life as that performed by clathrin. The self-assembly of COP-II into cages causes budding of vesicles from the endoplasmic reticulum for fusion with the first Golgi leaflet of the Golgi apparatus. Unlike clathrin, COP-II monomers act as half-arms in the assembly of cages with 4valent vertices and faces that are triangles,

squares and pentagons. Two prominent cage shapes are the cuboctahedron and the icosidodecahedron, but it self-assembles into other cage structures as well. Because COP-II provides half-arms instead of vertices, and because COP-II creates cages with 4valent rather than 3valent vertices, the explanation for which cages it can self-assemble is different from the one we have given for clathrin. We believe we have that explanation but have more work to do to prove that explanation.

4. **Viruses are another type of molecular cage.** We collaborate with investigators in the Electron Imaging Center for Nanomachines (EICN) on use of cyro-electron microscopy (cryoEM) to obtain whole virus structure at very high resolution, in some cases down to 3Å. At this resolution, it is possible to identify amino acids, and with the aid of software, to place all of the atoms, hence atomic resolution. The advantage of cryoEM is that we are able to obtain structures of proteins in their native environment, that is, within the whole virus. X-ray crystallography can achieve as good or better resolution, but generally only of individual proteins or parts of individual proteins that are able to be crystallized and have been taken out of their native environment. We have used structures from cryoEM to explain the structure of a bullet-shaped, helical, single-stranded RNA virus (Ge et al., 2010), the nature of the binding and fusion proteins in the envelope of an icosahedral virus with a genome of ten segments of double-stranded RNA (Zhang et al., 2010), and that atomic structure of the proteins that hold adenovirus from bursting under the pressure of its genome of double-stranded DNA (Liu et al., 2010). We have a paper under review on dengue virus, in which we describe several pH-sensitive steps in its maturation and exposure of its fusion peptide at the time of infection. We are currently working on a paper on the maturation of a herpesvirus, also a pressurized virus with a genome of double-stranded DNA, from a spherical shape to an angular shape.

5. **Mathematics of polyhedra.** With rare exceptions, although the fullerenes and some of these other cages are loosely described as convex polyhedra, these molecular cages have nonplanar faces. Thus, they are neither polyhedra nor convex. For example, we proved that among the infinite number of carbon fullerenes, only the truncated icosahedron (or soccer ball) (with 60 vertices) is a convex polyhedron. We realized that the nonplanarity was to some extent the consequence of a tendency for the interior angles (or bond angles) in faces to approach equality, for example, 120º in 6gons.

Taking a mathematical approach, assisted by chemistry software, we investigated whether it would be possible to obtain planar faces, thus convex polyhedra, while preserving the high symmetry – icosahedral, octahedral or tetrahedral – in 3valent cages composed of 5gons an 6gons, 4gons and 6gons, and 3gons and 6gons, respectively. That investigation has produced a new class of high symmetric, equilateral polyhedra. Surprisingly, the mathematics gives insight into why some bacterial viruses and animal viruses (like herpesvirus) with double-stranded DNA mature from a spherical shape to an angular shape. That said, with just a handful of major classes of polyhedra – the Platonic, Archimedean, Catalan, Johnson and rhombic – the contribution to mathematics is more significant than any application.

We are now using this work as a model to investigate whether we can create still more new classes of polyhedra.