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The fuzzy image

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ABSTRACT

This article celebrates the variety of Don Caspar's research interests, with particular focus on those scientific investigations beyond the structural biology of viruses for which he is often associated. These lesser known, seemingly backwater projects, allow us to build up a portrait, in both word and image, of this prolific and creative scientist. Exploration of his ideas will reveal a close connection to other structural thinkers and artists throughout history, most notably the 17th century astronomer Johannes Kepler.

1. Introduction

The term *Festschrift* perfectly captures the spirit of this special journal issue, which is to celebrate the work of Don Caspar. This term has no pithy translation to an English word, for like many German words it is actually a phrase, loosely translated as party-writing or celebration-writing. Here is another German phrase, which I believe also helps us to understand and appreciate Caspar's scientific work,

Ist das unscharfe nicht oft gerade das, was wir brauchen?

Literal translation:

Isn't the indistinct one [e.g., photograph] often exactly what we need?

which could be translated into modern American-English as,

Sometimes the fuzzy image is just what we need

Written by Wittgenstein in his *Philosophical Investigations* (Wittgenstein, 1953) this phrase was meant to convey the philosophical proposition that some concepts/ideas/notions/terms cannot, and indeed should not, be made precise or fully distinct. As part of this Caspar *Festschrift* I would like to use this phrase of Wittgenstein's as a linchpin, or anchor, to my own understanding and appreciation of Don's scientific oeuvre. This will lead to a scientific portrait, in both word and image. The image (in the final form shown in Fig. 9) may be familiar to some, since it has appeared over the years as a sort of an unofficial coat-of-arms for Don Caspar. As for the words, any portrait necessarily reflects the hand holding the brush. My written account is drawn mostly from the period I spent working as a graduate student with Don, in the late 1980's. Nonetheless, most readers will recognize the likeness.

To set a sort of baseline, the first section of this article briefly recounts my understanding, as a physicist, of the celebrated 1962 work on the principles of virus construction. From thereon, this paper celebrates Don Caspar's less appreciated scientific projects. Exploration of these ideas will reveal a close connection between Don and other structural thinkers in history, most notably the 17th century astronomer Johannes Kepler.

The sections which follow are fairly self-contained,

- Quasi-equivalence
- Kepler and Polyoma
- Diffuse scattering and protein dynamics
- Molecular graphics
- Quasi-crystallography
- Portrait the Scientist as an elder man

so impatient readers can sample or skip as they wish.

2. Quasi-equivalence

Sometimes the inexact rules best define the game

Caspar and Klug's theory of virus structure and assembly (Caspar and Klug, 1962) is understood as a masterpiece, a sweeping attempt to answer a biological problem in terms of rigorous principles of mathematics and physics. The title reflects and announces such: *Physical Principles in the Construction of Regular Viruses*. Not only structural biologists, but historians and philosophers of science have praised "The Caspar-Klug theory of virus

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structure, a theory that remains one of the simple, broad, and beautiful mathematical generalizations in biology" (Morgan, 2006).

When Don poached me from the physics department at Brandeis (wisely convincing me to stop studying string-theory and quantum field theory) the 1962 *Physical Principles* paper was the first I was advised to read before stepping into his Rosenstiel Center lab. Many in the Brandeis physics department secretly mocked my decision to leave the physics building for the "medical" building on campus, for much biophysics and biomedical research was considered "fuzzy physics" which employed "fuzzy math," presumably because it didn't begin all reasoning with the Schrödinger equation. Yet, this young mathematical physicist was pleased to find such phrasings in the 1962 paper as "self-assembly is a process akin to crystallization and is governed by the laws of statistical mechanics" ... "there are only a geometrically limited number of kinds of [virus] symmetry" ... "it is possible to characterize the structure of the virus by a small set of accurately determined numbers" ... "lowest energy structure" ... "essential geometric principles" ... and countless references to "symmetry," "principles," "theory," as well as equations ($P = h^2 + hk + k^2$), and invocation of obscure geometric theorems, drawn from equally obscure references such as *Lagerungen in der Ebene auf der Kugel und im Raum* (Toth, 2013), a book incidentally published in the same year, and language, as Wittgenstein's book.

When I first sat down to discuss possible thesis projects with Don, I proudly recited for him all of my favorite passages quoted above. Don politely brushed these aside, and began to explain (slowly, for about 3 hours) why I had missed the important message of his work. As important as this early theory was for laying down rigorous foundations for structural biology, it was what the theory left *inexact* which is just as, if not more, important.

> Any ordered structure, whether it is a crystal or a virus, will have some type of well-define symmetry. However... an ordered structure built of complex molecules such as proteins, need not have all identical molecules in *exactly* identical environments. The important point is that the lowest energy structure will have the maximum number of most stable bonds formed – and this may be physically realized, as in icosahedral virus shells, by quasi-equivalent bonding of identical units. These physical considerations have led to an extension of traditional concepts of symmetry, more specifically applicable to highly organized biological structure (Caspar and Klug, 1962).

One of the contexts for Wittgenstein's maxim ("Sometimes the fuzzy image is just what we need") was in understanding the concept of a game, where the philosopher argued there must inevitably be inexactness in the rules which define a game. "One might say that the concept 'game' is a concept with blurred edges" (Wittgenstein, 1953). If virus construction and self-assembly is a game, with molecular pieces moved according to natural rules, then the truly insightful idea in the 1962 *Physical Principles* paper is that biology allows– nay, requires– a blurred set of rules. Quasi-rules.

> We must drop the insistence on strict mathematical equivalence, but retain its physical essentials... bonds may be deformed in slightly different ways in the different, non-symmetry related environments. Molecular structures are not built to conform to exact mathematical concepts but, rather, to satisfy the condition that the system be in a minimum energy configuration (Caspar and Klug, 1962).

Indeed, besides accounting for the fuzziness (*unscharfe*) found in biological structure, the term "quasi-equivalence" itself is an example of the fuzzy. As Lee Makowski explains,

> I asked Don Caspar what 'quasi-equivalence' means. I didn't like the answer he gave me then, and I still don't like it. He said that it was unwise to define a word too precisely, because once you did it became very much less useful. With that, he just turned around and walked away, leaving me to wonder just what quasi-equivalence did mean. It may have been the shortest conversation I ever had with him (Makowski, 1998).

Although quasi-equivalence was the prototype, we shall see that many of Caspar's subsequent structural studies continued inside scientific territory where "it was unwise to define a word too precisely.".

3. Kepler and Polyoma

Sometimes the imperfect model is the correct one

Anyone vaguely aware of the work of Johannes Kepler will notice an obvious connection between Caspar and Kepler. The geometric figures in Don's papers, the polyhedral models which clutter his office, all echo Kepler's obsession with the Platonic solids (e.g., Compare Fig. 8 in the 1962 *Physical Principles* paper with the illustration from Proposition XXVIII in Book II of Kepler's 1619 book *Hamonices Mundi*). But the affinity between Caspar and Kepler goes even deeper, into the way these two men dealt with the rise and fall of their own scientific theories.

When I first entered Don's lab in the 1980's, there was still a buzz in the Rosenstiel Center about the Polyoma story. This puzzled me at first, that both the lab and its PI would be excited about the demise of their own theory. Most know the story. Though wildly successful, the original Caspar-Klug geometric theory of virus structure contained a damning prediction, "In this way, each hexamer has six nearest neighbors and each pentamer has five nearest neighbors. This close packing is a necessary consequence of the clustering about the vertices of the plane triangular net" (Caspar and Klug, 1962). This prediction proved true in all subsequent virus structures discovered over the next twenty years, even amidst a period of immense growth in structural biology, including the rise of synchrotron sources and the protein data bank. Then came new data, from Polyoma virus (Rayment et al., 1982). The best summary of this data's meaning was that emblazoned (in all-caps) on the cover of *Nature* magazine: ALL PENTAMER VIRUS CAPSID. What makes the story lore, of course, is that this data was collected and published, not by some competing research lab, but by Ivan Rayment in Don's own lab.

One day while we dined outside on a campus bench with sack-lunches, I asked Don why it didn't bother him that his perfect theory ended up being false, replaced by an *imperfect* model, a less beautiful – and he interrupted me as soon as he heard the term "beautiful." He laughed, "No, no, No. Polyoma is true. If a theory is true, then that's good. And if it's true and good... it *must* be beautiful." Then he talked some more, about the philosopher Plato, the poet Keats, on goodness, truth and beauty, on and on for another two or three hours sitting on the bench, often circling back to other historical characters such as Albrecht Dürer, and especially Johannes Kepler.

Indeed it is instructive to compare the Polyoma story with the story of Kepler's theory of the solar system. In Kepler's majestic work *Mysterium Cosmographicum* (1596) he was able to successfully account for the known structure of the entire solar system. His beautiful model nests the five Platonic polyhedra inside each other (Fig. 1). In each of the six available spaces defined between each pair of polyhedra, there exists a celestial sphere containing one of the six planets (Mercury, Venus, Earth, Mars, Jupiter, Saturn. The other planets being unobserved and unknown at that time). Remarkably, this purely geometric model accounts for both the