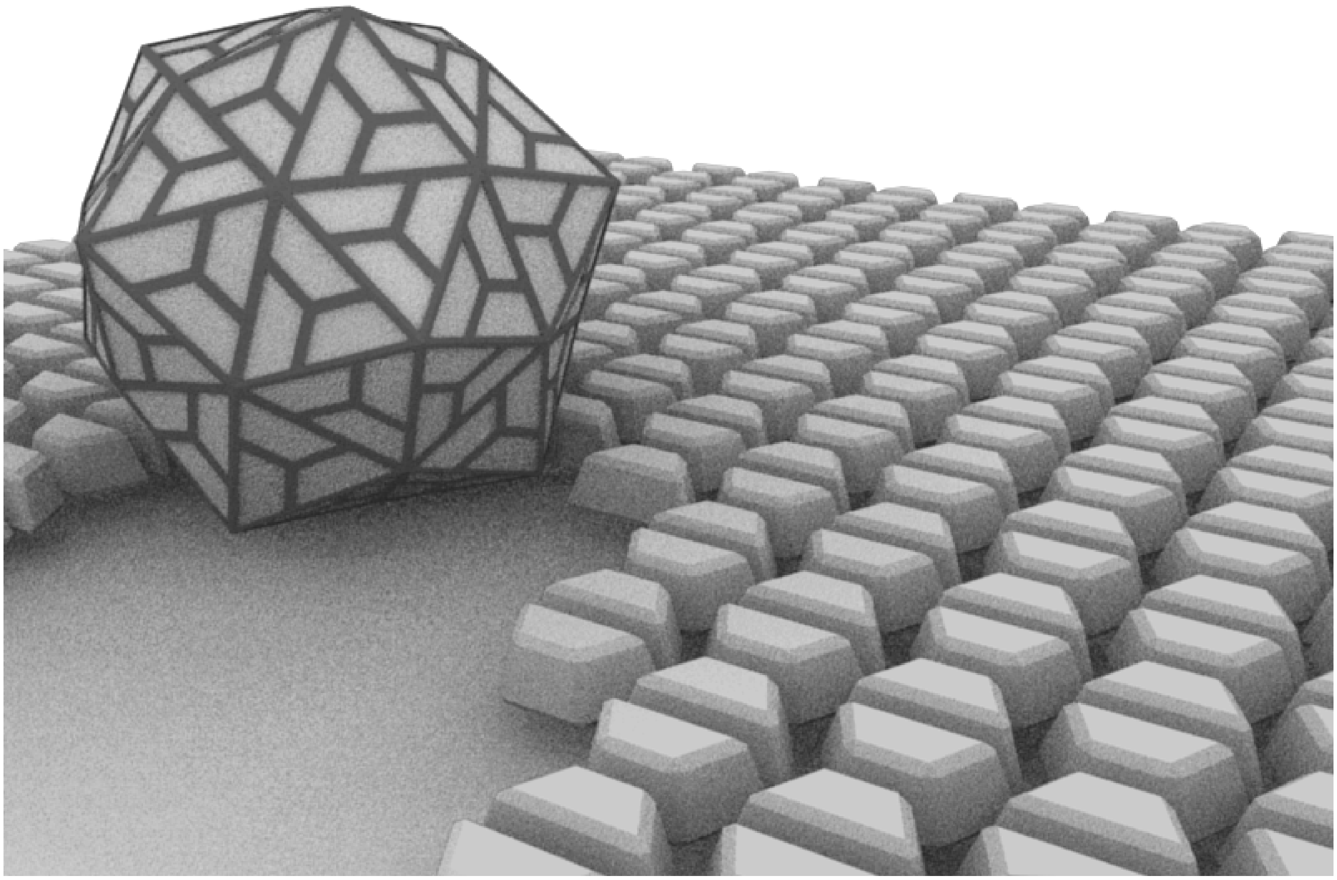
Nanotechnology of the Virus Capsid



(My rendition of a scanning electron micrograph of nanofabricated silicon subunits and an assembled silicon capsid)

A short proposal aimed towards
the rational design and production of
self-arranging nanoparticles from first principles.

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First proposed: 2010

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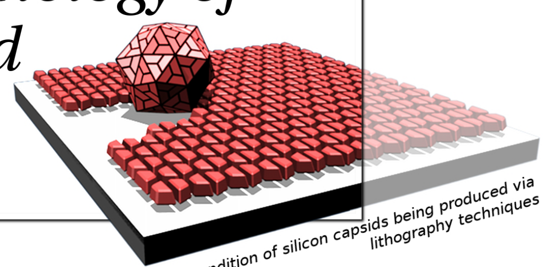
A rendition of silicon capsids being produced via lithography techniques

SUMMARY: Spherical capsids are nanometer-scale virus armors formed from a large number of self-assembling protein subunits. Currently, scientists are attempting to utilize capsids as vaccines, molecular scaffolds, and other medicine-related applications. I propose to apply our recent understandings of theoretical capsid design (Fig. 1) to the construction of completely artificial capsids by soft lithography techniques.

Gleaning insights from spherical capsids—nanometer-scale protective virus shells formed from a number of protein subunits—may allow for unique solutions to problems in biomedical and materials sciences. Possible examples of such applications include capsids designed to (1) attack cancerous cells, (2) cleanse grease-stricken arteries, and (3) pose as scaffolds for hydrogen-gas-producing nano-factories. All of these applications are unrealized but approachable, especially with a thorough understanding of how the capsid forms. My studies showed that the structure and function of a large number of natural capsids are underlined by simple mathematical rules, enabling the compilation of canonical capsid design principles. It is my hope that, with our new theoretical understandings, many new and exciting applications will soon be realized.

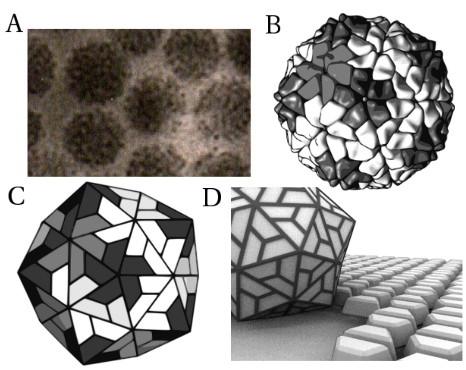

Fig 1. Geometric concepts and models (C) gleaned from electron microscopy (A) and crystalography (B) data may be useful in the design and construction of completely artificial *ab initio* capsids.

Here I propose to exploit the geometric nature of virus capsids (Fig. 1) by designing artificial ones from materials like silicon and porcelain. The need for biomimitic nanostructures is especially important as replacements of natural capsids, since proteins are linear folded polymers that, although efficient at what they do, are notoriously difficult to commandeer by protein design or modification techniques; certainly, the modification of natural subunit-subunit interactions are possible and useful, but their utility is limited, and drastic changes to protein functionality has been shown to be often unsuccessful. I propose an iterative cycle beginning with theoretical capsid design and ending with the mass-produced nanoassemblies displaying novel functionality.

These goals cannot be achieved alone but through exciting collaborations with angström- and nanometer-oriented scientists, which I believe, will allow for the confluence of theory, biology and nanofabrication technologies into solutions crucial to the rapid design and production of therapeutics and assemblies that may better the human situation.

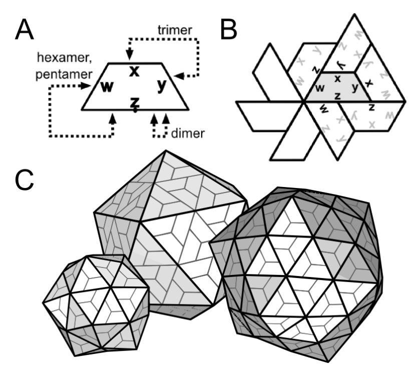

Fig 2. Rules for formation of specific virus capsids (C) are encoded within specific subunit-subunit interaction rules (A,B), along with set planar angles of interaction (Mannige & Brooks, 2010).

Subunit Properties. Capsid subunits must have five edges (i.e., five interacting neighbors) represented commonly by the ``bisected trapezoid'' (Fig. 2a; also see *Fig. 5* in Mannige and Brooks, 2008 and *Fig. 3* in Mannige and Brooks, 2009). Those edges must partake in three distinct subunit-subunit interactions (dotted arrows in Fig. 2A) allowing for the formation of dimers, trimers, pentamers and hexamers (e.g., Fig. 2B) that come together to form an icosahedrally symmetric structure (the capsid). We will start with designing artificial capsids by mimicking this trapezoidal subunit shape and bonding pattern.

Creating inorganic virus-like particles. The steps involved in producing completely artificial capsids will require iterations of the following: (1) subunit design, (2) subunit fabrication, and (3) testing via scanning/transmission electron microscopy.

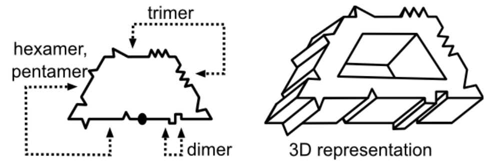

Fig 3. Complementary Interface etching may allow for the encoding of rules of subunit-subunit interaction within an artificial subunit.

Design. From our geometric understanding of the requirements of subunit-subunit interactions, we can design a trapezoidal subunit with etched interfaces (Fig. 3), where geometrically complementary interfaces will interact to form pentamers, hexamers, dimers and trimers – components of the final capsid (Fig. 2). Other features must also be imposed such as a mechanism to prevent van der Waals-driven subunit-subunit stacking by introduction of a cavity in the subunit (Fig. 3, right), etc. Finally, the planar angles with which the subunits interact can easily be modeled into the subunit by modification of specific interfaces, whereby closed assemblies of specific sizes will form.

Fabrication. After obtaining a sufficient subunit design (Fig. 4B), we will employ photolithography techniques to create a master stamp (Fig. 4D) followed by polydimethylsiloxane (PDMS) driven soft-lithography techniques pioneered by Whitesides and colleagues (Xia and Whitesides, 1998) to produce subunits in a quick and cheap manner (the turnaround time for subunit production may be ~24 hours from design, while the master can be used to produce a large number of cheap PDMS stamps reducing the cost to mass produce subunits).

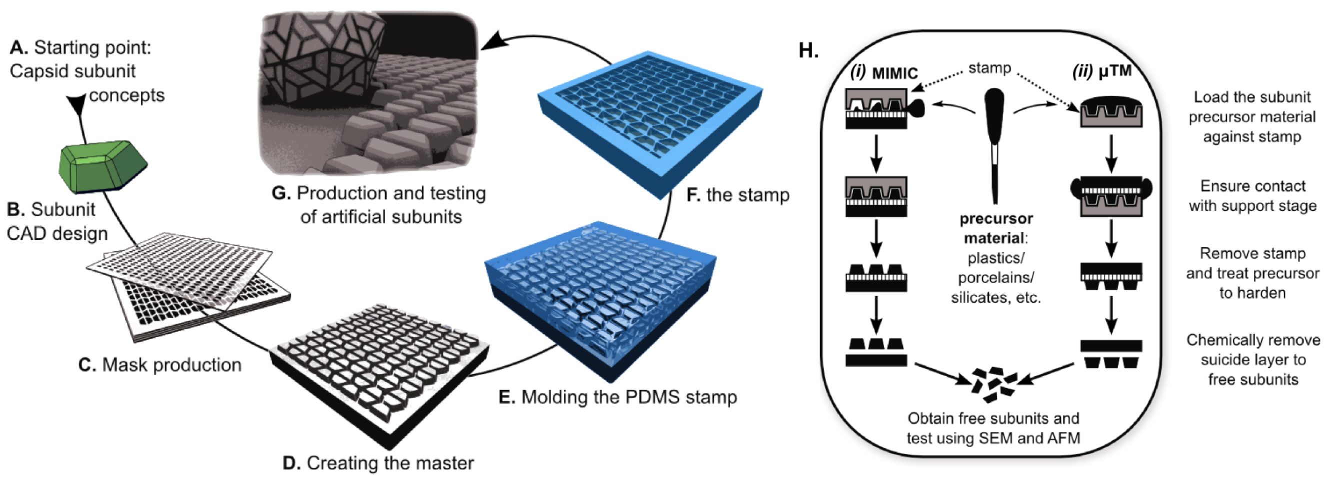

Fig 4. A-G outlines the general process of artificial capsid production using soft lithography techniques (Xia & Whitesides, 1998). Panel H represents the specific steps required for subunit fabrication from a PDMS stamp using *(i)* micromolding in capillaries (MIMIC) and *(ii)* microtransfer molding (µTM)

The size scale of the subunits will be contingent upon available lithography/soft-lithography technologies. Two specific methods for subunit production from PDMS stamps is delineated in Fig. 4H. Especially important in this step is the testing of a variety of subunit materials such as plastics, porcelains and silicates for properties conducive to proper assembly.

Once the development of such scaffolds is complete, the next step (and my final goal) is to help develop nano-to-angström resolution techniques for subunit modification, allowing for functional motifs to be specifically engineered into the artificial capsid.

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