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Article

Student Learning about Biomolecular Self-Assembly Using Two Different External Representations

Gunnar E. Höst,* Caroline Larsson,† Arthur Olson,‡ and Lena A. E. Tibell*

*Department of Science and Technology and †Department of Social and Welfare Studies, Linköping University, SE-601 74 Norrköping, Sweden; ‡Department of Integrative Structural and Computational Biology, Scripps Research Institute, La Jolla, CA 92037-1000

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Self-assembly is the fundamental but counterintuitive principle that explains how ordered biomolecular complexes form spontaneously in the cell. This study investigated the impact of using two external representations of virus self-assembly, an interactive tangible three-dimensional model and a static two-dimensional image, on student learning about the process of self-assembly in a group exercise. A conceptual analysis of self-assembly into a set of facets was performed to support study design and analysis. Written responses were collected in a pretest/posttest experimental design with 32 Swedish university students. A quantitative analysis of close-ended items indicated that the students improved their scores between pretest and posttest, with no significant difference between the conditions (tangible model/image). A qualitative analysis of an open-ended item indicated students were unfamiliar with self-assembly prior to the study. Students in the tangible model condition used the facets of self-assembly in their open-ended posttest responses more frequently than students in the image condition. In particular, it appears that the dynamic properties of the tangible model may support student understanding of self-assembly in terms of the random and reversible nature of molecular interactions. A tentative difference was observed in response complexity, with more multifaceted responses in the tangible model condition.

INTRODUCTION

How does hemoglobin form? If you pose this question to a biochemistry student, it is not unlikely that he or she will respond either by describing synthesis and folding of the individual proteins that make up this complex or by explaining how intermolecular forces hold the subunits together. Clearly, this story would be missing a crucial event, namely how the subunits actually come together to form a protein complex. How do the subunits "find" their correct positions? This enigma is explained by the extremely general principle of molecular self-assembly.

Self-assembly is a term that refers to processes in which higher-order structures form spontaneously and reversibly as a result of random interactions between the constituent self-assembling components. Most biological complexes, including well-known structures such as virus capsids, ribosomes, and cell membranes, form by processes that involve self-assembly. Not only is self-assembly essential to explain formation of biomolecular complexes in cells, but knowledge of self-assembly may be of direct practical use for nanotechnology research and development (e.g., Lindsey, 1991; Whitesides *et al*., 1991). The central importance of this concept is further supported by an ongoing concept inventory project (Howitt *et al*., 2008; Sears, 2008), in which self-assembly is identified as one of nine "big ideas" that define the overarching conceptual content of the molecular life sciences field.

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Address correspondence to: Gunnar E. Höst (gunnar.host@liu.se).
Conflict of interest statement: Arthur Olson is a founder of, and holds one-third interest in, a start-up science education company, Science Within Reach, LLC, incorporated in the state of California. The company has begun to manufacture and sell the self-assembling virus model described in this paper as the first product. No promotion of this product to the exclusion of other potential similar products should be construed.

Despite its proposed importance, the principle of self-assembly seems to be almost absent from the science education literature. For example, apart from the occasional exception (e.g., see Pollard and Earnshaw, 2008), it is our experience that biomolecular textbooks rarely explain this principle. In addition, there appears to be little empirical work done on studying student learning about and understanding of molecular self-assembly in the science education research literature, although some descriptions of external representations of self-assembly have been published (e.g., Jones *et al.*, 2006). The present study was initiated in response to this, in our view unsatisfactory, situation. In the following, we describe a study on student learning of self-assembly in a group exercise supported by external representations.

Potential Challenges for Learning about Self-Assembly

Although no studies on student learning about and understanding of self-assembly have been published, some clues to potential challenges may be obtained by considering difficulties with related topics. To understand the process of self-assembly, students need to integrate several molecular concepts. Examples of such concepts include randomness, the kinetics and thermodynamics of noncovalent interactions, and the structural and chemical complementarities of biomolecular interactions. Students' difficulties in learning individual concepts may give an indication of potential challenges for conceptualizing self-assembly. In this regard, science education research has found that upper secondary students may encounter difficulties related to some of the concepts involved in the self-assembly process. Moreover, some of the inherent characteristics of molecular self-assembly (e.g., randomness) may be so-called threshold concepts, which are particularly difficult for learners to grasp (Meyer and Land, 2003; Ross *et al.*, 2010).

At the molecular level, self-assembly proceeds via random encounters between entities, which may then interact to form complexes. Several studies have reported on students' difficulties in understanding the particle nature of matter (Harrison and Treagust, 2002), in particular the intrinsic motion of particles and their interaction with other particles (Novick and Nussbaum, 1978). Random molecular motion is also an essential factor in the explanation of diffusion, a concept that has been found challenging for students (Friedler *et al.*, 1987; Odom, 1995). Garvin-Doxas and Klymkowsky (2008) have reported a wide occurrence of alternative conceptions specifically related to the random aspects of diffusion. In their work, only a small minority of students included randomness when explaining diffusion, and most students described diffusion as a directional process that occurs only in connection with concentration gradients. Chi (2005) suggested that diffusion is more difficult to learn than directional flow, partly because it is based on random interactions. In fact, researchers have observed that alternative conceptions about diffusion appear to be resistant to traditional teaching interventions (e.g., Odom and Kelly, 2001).

Fundamental thermodynamics underlies most molecular concepts and is thus an important prerequisite for building many related concepts. Therefore, difficulties with thermodynamics could become obstacles for students in understanding the self-assembly process. Furthermore, confusion concerning thermodynamic terms (Ochs, 1996) and the inherent complexities of thermodynamic analyses of biomolecular interactions (Cooper, 1999) may provide additional challenges. Indeed, thermodynamics has been found to be a challenging topic for many students, and difficulties related to, for example, equilibrium, reversibility, and Gibbs energy have been reported (Banerjee, 1995; Thomas and Schwenz, 1998).

The Learning Process and Small-Group Learning

This study aligns itself with a constructivist view of learning. Students are seen, in this framework, as actively learning by integrating their experience in the classroom with their prior conceptual understanding (Ausubel, 1968). In addition, we acknowledge the important contribution to this process from learners' interactions with persons in their surroundings. The literature on teaching strategies reveals several benefits of using peer interaction in teaching science. For example, in a meta-study of undergraduate science, mathematics, engineering, and technology education since the 1980s, Springer *et al.* (1999) showed that small-group learning can have a favorable impact on student achievements and attitudes. Collaborative learning, small-group learning, and approaches such as problem-based learning are all similar teaching strategies for enabling peer interaction/exploration. Literature in this field suggests that collaborative-learning processes may activate students' prior knowledge, which, in turn, facilitates the processing of new knowledge (Schmidt and Moust, 1998). The work presented here is founded on the hypothesis that peer interaction in relation to external representations can benefit learners in fostering appropriate understandings of complex science concepts such as self-assembly.

External Representations for Learning Self-Assembly

In addition to the potential conceptual difficulties of self-assembly, student learning is also challenged by the unobservable nature of the molecular scale (Tibell and Rundgren, 2010). Diagrams, models, and other forms of external representations are therefore an essential part of science and science teaching (e.g., Gilbert, 2008). Although using external representations in teaching certainly is no guarantee for successful learning, such representations are nevertheless important tools for learners' meaning-making and can assist students in construction of mental models of a studied phenomenon (Schönborn *et al.*, 2002). Experience in using external representations is also important for students' abilities to participate in a scientific community of practice. In fact, experts depend on using external representations to elaborate research ideas and search for explanations behind empirical observations (Kozma *et al.*, 2000), which can have a direct impact on the progress of science (e.g., Watson and Crick, 1953). The most common type of external representation in teaching and learning molecular science is probably the static image or diagram. However, although molecular life sciences textbooks often contain pictures of processes that actually involve self-assembly, this step is seldom explicitly shown. One example of a textbook image that does depict self-assembly, by showing the formation of a virus capsid, is given in Figure 1A (Alberts *et al.*, 2008).

Another type of external representation used in molecular education is the tangible or hands-on model. Researchers

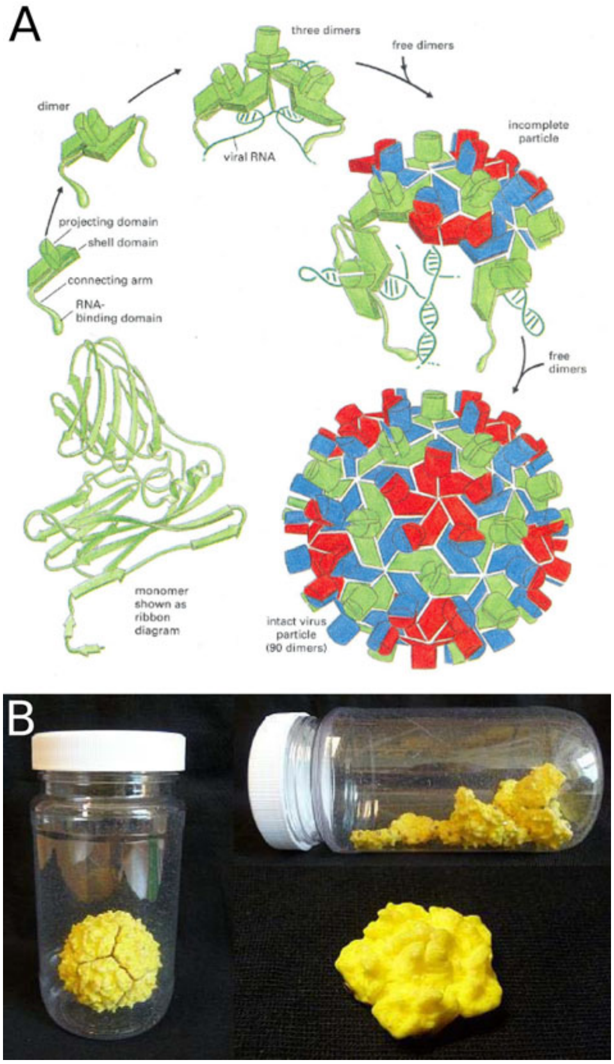

Figure 1. External representations used in the present study. (A) Image depicting the process of self-assembly of a tomato bushy stunt virus capsid. (B) Interactive tangible model of a poliovirus capsid, consisting of subunits with magnets attached. Students can interactively investigate self-assembly of the capsid by shaking the subunits in a container and observing the build-up of the model as the pieces come together.

have found that students can benefit from using tangible models when learning about biomolecular topics (e.g., Roberts *et al*., 2005; Rotbain *et al*., 2006; Harris *et al*., 2009). A classic example of such a tangible model, used in chemistry education since the beginning of the 20th century, is the representation of the atomic configuration of a molecule using balls and sticks or space-filling spheres (Petersen, 1970). Since then, many educational researchers have investigated the impact of these types of tangible models in teaching and learning about molecules (e.g., Copolo and Hounshell, 1995). Several studies suggest that tangible models may provide opportunities for students to learn molecular concepts. Gabel and Sherwood (1980) propose that manipulation of a tangible model can enhance students' chemistry achievement in the long term, and Dori and Barak (2001) have found that using a combination of virtual and tangible models can enhance student understanding of molecular structures in learning chemistry and develop students' spatial abilities. Roberts and coworkers (2005) evaluated the use of various external representations, including tangible models, as part of a protein course. They reported that, out of seven learning tools, the students perceived the tangible models to be the most helpful for learning about protein structure and function.

A few examples of tangible models of self-assembling systems have been reported in the science education literature. Among these are LEGO bricks with magnets attached to them to construct systems that self-assemble in various ways (Campbell *et al*., 2001; Jones *et al*., 2006). Other described self-assembly models employ capillary forces between objects such as soda straws (Campbell *et al*., 2002) or breakfast cereals (Dungey, 2000) on the surface of a liquid to accomplish self-assembly of extended structures. The close packing of atoms in metals has been represented using soap bubbles on a water surface (Geselbracht *et al*., 1994). The systems in the studies above concern self-assembly in two dimensions, and none represents the self-assembly of a biologically relevant system. Olson *et al*. (2007a) have described a tangible model of self-assembly of a poliovirus capsid (see Figure 1B). No evaluations of the educational impact of the tangible models above are available.

Although much is known about molecular science learning using external representations, the apparent absence of educational research on self-assembly instruction and learning calls for empirical studies. In particular, the dynamic and potentially difficult nature of the complex concept of self-assembly may present a significant challenge for educators.

Aims and Research Questions

Given the above motivation, the overall aim of this study is to investigate student learning of self-assembly using external representations to support discussions in a peer-interaction context. More specifically, we raise the following two research questions:

1. What is the impact of using external representations in a group exercise on student knowledge of self-assembly?
2. Are there any differences in learning outcome between using a tangible model and an image in a group exercise?

METHOD

Study Design

The differences in the impact of using two different external representations (a tangible model and an image) on learning about self-assembly in a group exercise were investigated using a true experiment design (Robson, 2002). A mixed two-factor design was used in which the first factor, external representation (tangible model/image), was a between-groups factor, while the second, time (pretest/posttest), was a within-groups factor. Thus, the group exercise learning context was kept constant, while the external representation was varied between groups. This design was used to allow any differences in outcome between using the two external representations in the group exercise to be revealed. It should be noted that to the extent that the two external representations

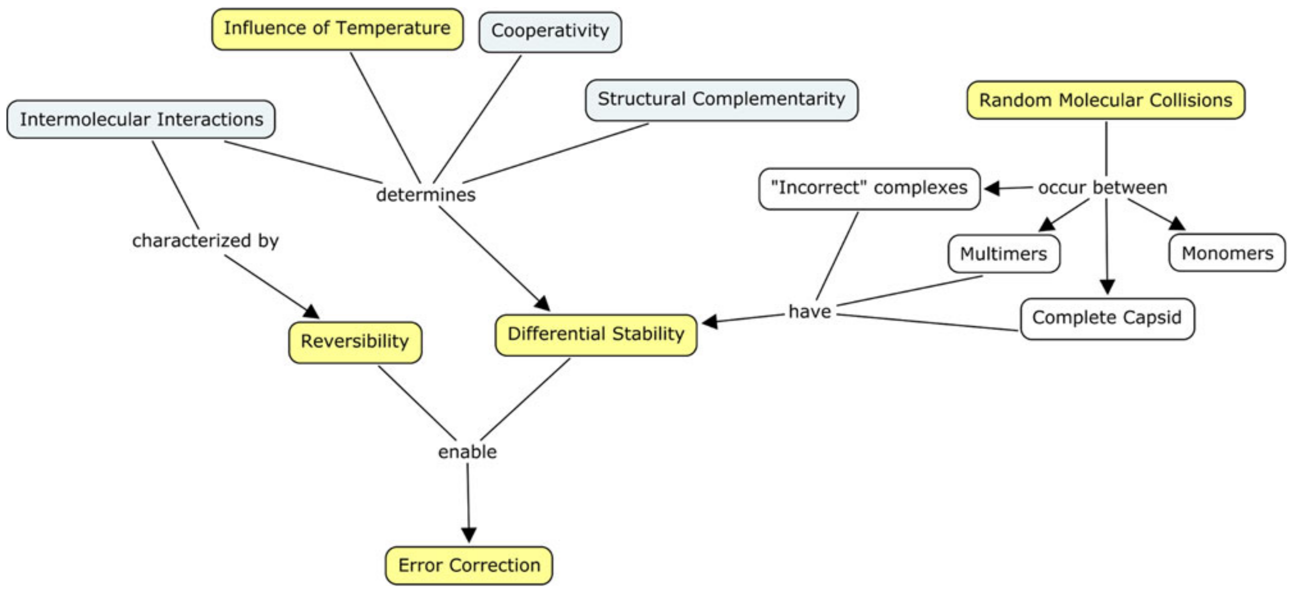

Figure 2. A concept map of self-assembly composed of interlinked facets. The dynamic facets that are the focus of the present study are shown in yellow, while other facets are gray. The white boxes represent different molecular complexes. (Figure constructed using the CmapTools software from Florida IHMC [cmap.ihmc.us].)

yield identical outcomes, the design does not allow these effects to be disentangled from the overall influence of the group exercise. Written pre- and posttest data and audio recordings of group exercises were collected. The two different external representations (i.e., the tangible model and the image) were used as focus instruments in group exercises. The current study reports on findings from the written pre- and posttest data. The study used a mixed-methods approach to allow triangulation of findings. Proper procedures were followed to ensure the participants' confidentiality and personal integrity. Although the exercise was part of the mandatory curriculum, each individual student decided whether the data he or she generated could be included in the research.

Conceptual Analysis of Self-Assembly

The research design was initiated by performing a conceptual analysis of the self-assembly process, summarized and expressed in a concept map (Figure 2). The conceptual analysis procedure consisted of specifying and describing the principles that are necessary to incorporate in a scientific explanation of self-assembly. The principles underlying the overarching concept self-assembly were expressed in the form of conceptual elements that will be referred to as "facets" in the following (cf. Minstrell, 1992). Finally, relationships were assigned between the identified facets.

The mechanism of self-assembly in molecular systems is based on several underlying principles. In addition, the term self-assembly is used somewhat differently across the scientific community to describe phenomena in which order arises in systems with no external control. Some confusion might be caused by the similarity between self-assembly and the related term self-organization, which is often used for pattern formation in nonequilibrium systems that require an energy source (Barth, 2007; Halley and Winkler, 2008). Others use the term self-assembly for all processes of autonomous pattern formation from components but distinguish between several subtypes of self-assembly (Lindsey, 1991; Whitesides and Grzybowski, 2002). In this paper, self-assembly is defined as pattern formation in systems that tend toward equilibrium (Halley and Winkler, 2008). The scientific literature on self-assembly is very extensive and could not be reviewed in its entirety. However, consulting the literature in search of key references yielded the basis for the concept map in Figure 2, described in the following. Five dynamic facets of self-assembly, shown in yellow boxes in Figure 2, were given particular attention in this study (see Table 1).

Among the defining features of self-assembly is that it proceeds via *random molecular collisions* between subunits (Pollard and Earnshaw, 2008) and that the process operates in a reversible (*reversibility*) and near-equilibrium manner that allows for *error correction* (Olson *et al.*, 2007a; Whitesides *et al.*, 1991). The reversibility of the process means, in the present case of virus capsid formation, that both correctly formed virus particles and "incorrectly" formed complexes (i.e., intermediates that are off the pathway to complete capsids) can dissociate. Error correction is a consequence of the higher stability of correctly formed complexes compared with incorrect complexes of the same size, from which the incorrectly bound subunit dissociates easily. The stability of the resulting structure is ensured by cooperatively reinforcing intermolecular interactions between structurally complementary surfaces (Williamson, 2008). The assembly process is driven by *differential stability*, wherein the resulting structure is more stable than the components and intermediate complexes (Endres *et al.*, 2005). The process is dependent on temperature, with an increased proportion of incorrectly assembled complexes more probable at lower temperatures (*influence of temperature*; Nguyen *et al.*, 2007).

It is possible that the presented view of self-assembly could be further improved and extended, but the main features of

Table 1. Definitions of the facets of self-assembly on which the present study focuses

Facet	Definition
Random molecular collisions	Self-assembly proceeds through completely random collisions between subunits.
Reversibility	In self-assembly, interactions form and break continuously.
Differential stability	Multimeric complexes of subunits that form during self-assembly are increasingly stable as the number of subunits in the complex increases.
Influence of temperature	The stability of both correct and incorrect complexes during self-assembly decreases with increasing temperature, and vice versa.
Error correction	Self-assembly is self-correcting, because incorrectly formed complexes have a low stability, and all interactions are reversible.
Structural complementarity	The binding of subunits to one another is stabilized by the multiple interactions made possible by the complementarity of the interacting surfaces.

this description are clearly fundamental and supported by the scientific literature. The complexity of the concept map was purposefully limited to exclude facets not considered to be critical for understanding the fundamental molecular mechanisms that enable self-assembly. For example, facets related to the kinetic properties and concentration dependence of the process and the potential occurrences of irreversible steps (e.g., cleavage of covalent bonds) were excluded from the concept map.

Procedures

The study was conducted in the context of a practical group exercise integrated as a mandatory part of a biochemistry course at a Swedish university.

Sample. The participants were Swedish second-year university students (n = 32, 23 female and 9 male) studying either for engineering biology or chemical engineering degrees. The students had previously taken (and passed) an introductory biochemistry course, and it was therefore assumed that they shared a similar basic knowledge of protein structure/function and cell metabolism.

Group Exercise. A previously piloted written group exercise guide consisting of six tasks was used, structured as follows. Task 1 was to manually assemble the tangible model or to study the image. Following this, students were stimulated to discuss (task 2) how capsids form in vivo, (task 3) the effect of an increase in temperature, (task 4) the effect of a decrease in temperature, (task 5) potential errors during self-assembly, and (task 6) the limitations of the tangible model/image. A researcher assumed the role of a discussion initiator who initiated tasks and, if necessary, clarified task questions but did not participate in the exercises. Typically, the tasks were composed of a task initiation question (e.g., for task 2: "How is assembly achieved during virus production in vivo?"). Students then discussed the question using the external representations as focus instruments, and scripted follow-up questions were posed by the exercise initiator (e.g., "Do the subunits always assemble in the same way?"). Although the two external representations required slight variations in the guide (e.g., see task 1 above), the ambition was to treat both groups identically.

External Representations. Two different external representations were selected for this study, namely a tangible model and an image, both of which show the self-assembly of a virus capsid. The criteria for choosing these particular external representations were that they constitute two (out of very few) existing models that may be used in education, they display essentially the same process, and they differ in their properties. The tangible model, depicted in Figure 1B, consists of 12 identical pentagonal subunits with appropriately positioned magnets along their edges. Students can interactively investigate self-assembly of the complete capsid by shaking the subunits in a container and observing the build-up of the model as the pieces come together. Typically, this process can be completed within 1 and 5 min, but the assembly time is unpredictable. A video clip depicting this can be found in the supplemental material to a paper by Olson *et al*. (2007b). The image, depicted in Figure 1A, is a textbook illustration of viral self-assembly (Alberts *et al*., 2008). It depicts the self-assembly of virus capsid subunits around the genome of a virus. One protein subunit is shown in some structural detail, while the other subunits are represented schematically. Different colors are used to emphasize that identical subunits may have slightly different local environments (quasi-equivalence).

Pre- and Posttests. The pre- and posttests administered before and after the group exercise were designed to probe students' knowledge of self-assembly and how much confidence they have in their knowledge. Items based on five selected facets of self-assembly (yellow boxes in Figure 2) were constructed. These five dynamic facets were selected because they were expected to be the least well-known by the students. Whereas facets such as cooperativity, intermolecular interactions, and structural complementarity are also important, they are typically covered explicitly in introductory biochemistry courses. Following critical comments from four experienced biochemistry researchers, the probes were adjusted and piloted. The resulting test consisted of 11 probes (see Supplemental Material).

Ten close-ended items were included in the test, two for each of the five facets. They consisted of statements that the students responded to by rating their level of agreement or disagreement. The allowed responses were "I agree completely," "I agree somewhat," "I disagree somewhat," "I completely disagree," and "I don't know." This scale allows simultaneous evaluation of students' knowledge and level of confidence. One true and one false statement were included for each facet except for random molecular collisions, for which both statements were true in an effort to avoid teleological and/or anthropomorphic language in the test items. Identical items were used in the pre- and posttest. Any order effects were minimized by using two versions of the test that differed in item sequence and giving each student a different version on the pre- and posttest.

The 11th item on the test consisted of the following open-ended probe: "Imagine that you are going to explain the process of self-assembly to a small child that is not familiar with the appropriate scientific terminology. Describe how you would explain it." Specifying a child as the intended audience signaled to the students that their responses should be self-sufficient and not assume knowledge of biochemical terminology. The formulation was thus designed to stimulate the students to phrase their scientific understanding in everyday language. The purpose was to reveal the depth of intention in explaining self-assembly.

Data Collection. Each participant was randomly assigned to one of three groups in the tangible model condition ($n = 15$) or one of three groups in the image condition ($n = 17$). Each of the six resulting groups was composed of between four and six students. Immediately prior to the group exercise, students performed a pretest. The practical group exercises were then conducted. The exercises lasted for 20–30 min and were audio-recorded. A posttest was conducted immediately after the group exercise. The sessions were performed with each group physically isolated from other students during the exercise to avoid interference between groups.

Data Analysis

Quantitative Analysis of Close-Ended Pre- and Posttest Responses. Changes in student knowledge of self-assembly and their confidence in their knowledge were analyzed separately. The quantitative analysis was based on responses to the 10 close-ended test items, while responses to the open-ended test item were analyzed qualitatively, as presented in the subsequent section. Analysis of student confidence used a summed confidence score for the test items. This measure was calculated by awarding a score of one to responses in the "strongly agree" and "strongly disagree" categories, while other responses were awarded a score of zero. However, a significant intraclass correlation coefficient was observed for the confidence scores, indicating a nonindependence of confidence scores for students who were in the same group (Kenny *et al.*, 1998). Therefore, the confidence data was not analyzed further. A summed knowledge score for the 10 close-ended test items was used as a measure of students' knowledge. Knowledge scores were awarded to the pre- and posttest as follows. For each correct response to an item (i.e., agreeing with a correct statement or disagreeing with an incorrect statement) the student was awarded one point. Incorrect responses and responses in the "I don't know" category were given a score of zero. The intraclass correlation coefficient was found to be nonsignificant for the knowledge scores, indicating independence of knowledge scores for students who were in the same group (Kenny *et al.*, 1998). The Kuder–Richardson formula 20 (KR-20) reliability for the 10-item test was calculated as 0.58 in this study. This was acceptable, given that the items targeted multiple facets of the self-assembly construct. Changes in the measure of students' knowledge of self-assembly were assessed by [2×2] mixed analysis of variance (ANOVA) with two levels of the between-subjects factor external representation (tangible model/image) and two levels of the within-subjects factor time (pre- and posttest).

Qualitative Analysis of Open-Ended Test Items. The written responses to the open-ended items in pre- and posttests were analyzed qualitatively using qualitative content analysis (e.g., Graneheim and Lundman, 2004). The content analysis was systematic and was performed in two rounds (Kreuger and Casey, 2000), one deductive and one inductive. Using this approach, qualitative differences and commonalities among responses from students in the two conditions (tangible model and image) were identified.

In a deductive round of analysis, students' written responses were analyzed with respect to the five facets of self-assembly defined in Table 1. In doing so, expressions that conveyed facets were coded accordingly to allow a qualitative description of whether and how students included the underlying molecular phenomena in their explanations. Delving into the data indicated other interesting features of students' responses. These were analyzed inductively in two consecutive phases. In the first phase, any patterns in the written text were systematically coded. This resulted in categories that represented such patterns and contained statements that related to the same topic (Baxter, 1991). Thus, the inductively coded categories originated from the data material itself (Alvesson and Sköldberg, 2009). The second phase of the inductive analysis aimed at testing and verifying possible subcategories. The categories developed in this way were used as analytical tools to structure, interpret, and describe the findings in further iterative rounds of inductive analysis.

Attempts were made to increase the credibility of the qualitative data analysis by maintaining a dialogue concerning the labeling and sorting of the data between the involved researchers. Thus, the data corpus was read through several times and analyzed iteratively by three independent coders, and their analysis results and interpretations were compared. In most cases, the categories identified by different coders were the same or similar. In the few cases in which there were disagreements, the data were reanalyzed until agreement was reached and the final category descriptions established. According to Larsson (2009), qualitative data can be generalized through recognition of patterns. This is dependent on the reader's ability to recognize patterns in pieces of research that can assist interpretations in other situations, processes, or phenomena. For this reason, we aimed at providing a rich descriptive presentation of the qualitative findings.

RESULTS

Learning Outcome in Close-Ended Pre- and Posttest Items

Summed scores from the 10 close-ended test items were used as measures of students' knowledge. The learning outcomes of the group exercise was analyzed using a [2 × 2] ANOVA, which showed a main effect of time ($F(1, 30) = 23.03$; mean square error [MSE] = 44.3; $p < 0.001$; $p\eta^2 = 0.43$) and no interaction between time and model type ($F(1, 30) = 3.69$; MSE = 7.0; p = nonsignificant). Thus, the results of the quantitative analysis indicate that students in both conditions (i.e., tangible model and image) improved their knowledge scores between pre- and posttest and that there was no significant difference in learning gain between the two conditions (see Table 2).

Table 2. Mean knowledge scores and SDs of pre- and posttest by type of external representation[a]

	Tangible model ($n = 15$)		Image ($n = 17$)	
Time	Mean	SD	Mean	SD
Pretest	6.20	1.61	5.94	1.39
Posttest	8.53	1.77	6.94	1.60

[a]Possible mean knowledge score range: 0–10.

Students' Written Explanations of Self-Assembly

A qualitative content analysis of students' explanations was used to further assess how students' conceptual understanding of self-assembly was influenced by the group exercise. The responses varied in length, complexity, and depth of understanding. While some students gave responses that consisted of a single sentence, other students provided more elaborate descriptions. To provide readers with an idea of the variation in responses, we give the following examples of a short and a long response:

> "It is tiny, tiny pieces that are assembled into a bigger. They are put together like a jigsaw puzzle into a ball, and then it is finished." [Posttest written response, image model]

> "A lot of identical pieces of wall are formed, and for the virus to be functional these pieces must be assembled like a jigsaw puzzle into a round ball. All pieces can sit anywhere in the ball, but it only becomes a ball if they sit in the correct way. They are pulled towards each other like magnets and if they bind incorrectly they can detach and start over. When the ball is complete it is hardest to break." [Posttest written response, tangible model]

It was found that students' written pretest explanations did not reveal much prior knowledge of self-assembly (Tables 3 and 4). Thirteen students (13 of 32) did not attempt to explain what self-assembly is at all, and several students (eight of 32) gave explanations that were more or less irrelevant to self-assembly, for example, by describing other aspects of the virus's life cycle. Only four students (four of 32) included statements related to any of the dynamic facets in their pretest responses, in this case random molecular collisions, reversibility, and error correction.

Table 4. Number of facets per written open-ended response in pre- and posttest for students in the image ($n = 17$) and tangible model ($n = 15$) conditions

	Pretest		Posttest	
Number of facets	Image	Tangible model	Image	Tangible model
0	13	12	7	1
1	3	1	5	9
2	1	1	3	1
3	0	1	2	2
4	0	0	0	2
5	0	0	0	0
6	0	0	0	0

In comparison with the pretest responses, students' posttest explanations employed facets more often (Table 3). There was a qualitative difference between the two conditions in the number of times the facets were included in the posttest, with facets being more frequently included in the responses from the students in the tangible model condition than the image condition (Table 3). In addition, the tangible model condition had a lower fraction of posttest responses that did not include any facet compared with the image condition, and the most complex responses were found in the tangible model group, with some responses including four facets (Table 4). A descriptive account of the qualitative findings with example quotes is given below.

Random Molecular Collisions. Students in the tangible model condition included random molecular collisions in their explanation somewhat more often than did students in the image condition (Table 3). Only a single student in the image condition explicitly mentioned randomness, by

Table 3. Number of occurrences for facets in written pre- and posttest responses to an open-ended test item presented separately for the tangible model ($n = 15$) and image ($n = 17$) conditions[a]

Facet		Pretest	Posttest
Random molecular collisions	Tangible model	0	6
	Image	2	2
Reversibility	Tangible model	2	5
	Image	0	2
Differential stability	Tangible model	0	1
	Image	0	0
Influence of temperature	Tangible model	0	2
	Image	0	0
Error correction	Tangible model	1	4
	Image	0	3
Structural complementarity	Tangible model	3	7
	Image	3	10
Total	Tangible model	6	25
	Image	5	17

[a]Open-ended test item: "Imagine that you are going to explain the process of self-assembly to a small child that is not familiar with the appropriate scientific terminology. Describe how you would explain it."

introducing "Mrs. Chance," an anthropomorphic character who fits the pieces of a puzzle together. By contrast, three students in the tangible model condition included randomness in a way that more clearly connected it to the molecular process of self-assembly. For example, the following posttest response from a student in the tangible model condition conveys an understanding of the facet that is close to the definition in Table 1:

> And these larger pieces are going back and forth, crashing into each other. When they crash with each other they can bind.

Reversibility. Students in the tangible model condition incorporated reversibility in their responses to the open-ended test item more frequently than did students in the image condition (Table 3). All students, in both conditions, who included reversibility described that subunits might dissociate after binding, given that the binding is incorrect in some way, as exemplified by the following posttest response from a student in the image condition:

> When a virus is formed, small pieces are put together to form a larger complex. If one piece of the puzzle is wrong it is released and a new piece attaches.

In addition to references to incorrect binding, one student in the tangible model condition also stated in the posttest response that dissociation of correctly formed complexes (i.e., an intermediate on the pathway to a complete virus capsid) might occur at high temperatures (see *Influence of Temperature* below).

Differential Stability. Few students included reasoning wherein the stabilities of different complexes were compared (Table 3). Out of all participants, only a single student in the tangible model condition included this facet by stating that "when the ball is complete it is hardest to break" in the posttest response. No student included any explicit references to the term "stability" in a response.

Influence of Temperature. Inclusion of the facet influence of temperature was observed in the posttest responses from two students in the tangible model condition (Table 3). These statements referred to the effects of an increased temperature and did not consider the consequences of a lowered temperature. The following example, delivered by a student in the tangible model condition as part of an elaborate analogy between self-assembly and a group of people engaging in play, illustrates this:

> If it is warm you may not want to hold hands, even if you like your friend, and then you let go and run along.

Error Correction. Students in both the conditions incorporated error correction in their responses to the open-ended test item (Table 3). Here, an example is provided from the posttest of a student in the image condition:

> When pieces end up in the correct place they will more easily stay than if they end up in the wrong place.

Structural Complementarity. From the inductive analysis of the written responses, it was found that several students conveyed the important role that structural complementarities between subunits have in self-assembly (Figure 2). The descriptions focused on the features that underlie structural complementarity. In most cases, this involved making analogies to a jigsaw puzzle, such as the following posttest response from a student in the image condition:

> It [virus self-assembly] works like a jigsaw puzzle, for the various parts to be coupled together they must fit to each other.

Some students who introduced an analogy of structural complementarity did not elaborate on the connections between the analogical domains, that is, a jigsaw puzzle and a virus capsid protein complex. Instead, they seemed to rely on the analogy to be self-explanatory. The short and the long sample responses given previously in this section illustrate this.

DISCUSSION

This study addresses the lack of educational research on student understanding of self-assembly, which is an important concept in the molecular life sciences (Howitt *et al.*, 2008; Sears, 2008). If students are not aware of the principles behind self-assembly, they are essentially left in the dark with respect to how the fundamental process of molecular complex formation actually happens. Any doubts regarding the practical importance of familiarity with the concept for future molecular scientists should be alleviated by considering the importance of self-assembly in bottom-up approaches to nanotechnology (e.g., Lindsey, 1991; Whitesides *et al.*, 1991).

The results from the present study indicate that the participating students were not familiar with self-assembly. In particular, the many written pretest responses to an open-ended test item that did not include any explanation of self-assembly indicate that the students were unable to identify the relevant concepts and verbalize meaningful connections between them. A possible explanation is the apparent absence of self-assembly explanations from textbooks, with only very few biomolecular educational texts (e.g., see Pollard and Earnshaw, 2008) including more than a brief mention of the term, in our experience. This absence was reflected by some of the students in this study, who explicitly stated that the phenomenon had not been explained to them in previous courses. Although the size of the study group and the similar educational background of the students preclude generalizations of this finding to a wider body of students, the results motivate further investigation of students' knowledge of self-assembly in diverse educational settings.

In the following, the results from this study are discussed with respect to each of the two research questions.

What Is the Impact of a Group Exercise Supported by External Representations on Students' Knowledge of Self-Assembly?

Students in this study improved their knowledge scores after participating in external representation-supported group exercises. The collaborative-learning environment seems to provide a beneficial context for the students to engage and adjust their conceptual understanding with respect to the statements provided in the test. This finding is consistent with previous literature on small-group learning (Springer *et al.*, 1999). However, although the results indicate that students learned about self-assembly during the group exercises, it should be noted that the experimental design used in this study does not allow any conclusions to be made as to whether the group exercise learning intervention is more or less successful than other possible intervention formats could have been. Given that there are no previous investigations of student learning of self-assembly in the literature, the results presented here may serve as a starting point for future comparisons between diverse teaching–learning interventions.

In learning about self-assembly, the students faced the challenge of integrating experiences gained from participating in the group exercise with their prior molecular knowledge. While asking students to respond to propositions in the close-ended test items can uncover differences in knowledge, a deeper level of learning can be revealed through students' written explanations of self-assembly in the open-ended test item. Expressions that conveyed an understanding of the facets of self-assembly were used more frequently by the students in their posttest responses than in their pretest responses. This is further evidence that the group exercise has stimulated students to process the concepts into a cognitive structure they can verbalize in the context of an explanation of how self-assembly works, possibly by activating their prior knowledge of molecular mechanisms (cf. Schmidt and Moust, 1998).

It may be expected that understanding self-assembly is demanding, because the concept is composed of several other subconcepts, some of which are themselves known to be challenging, such as random molecular movement and thermodynamics (Novick and Nussbaum, 1978; Banerjee, 1995; Garvin-Doxas and Klymkowsky, 2008). Although some previous studies were made at the upper secondary level, it seems likely that the observed difficulties may also be experienced by students at the university level. In particular, the students in this study all have upper-secondary science studies as their educational background. It can be noted that only in a few cases did students include the thermodynamics-related facets differential stability, influence of temperature, and error correction. Possibly, this could indicate that students have difficulty in making coherent connections between any previously existing thermodynamic knowledge and their newly formed conceptions of self-assembly. It is less likely that the students were completely unaware of these three facets, because many were able to respond correctly to the close-ended test items related to these facets. We are not aware of other studies on student thinking concerning these facets, but it is probable that the students in this study had a previous understanding of these facets that had been developed in other contexts. For example, it is likely that the students had encountered temperature dependencies in relation to organic reaction chemistry and enzyme theory in the introductory courses taken prior to their participation in the present study.

Students' inclusion of facets in their open-ended responses were interpreted in terms of the depth and complexity of their self-assembly conceptions. It should be pointed out that in some cases it was difficult to interpret whether a student's response reflected a scientifically correct understanding of the facets or not. For example, one student referred to randomness by invoking a character called "Mrs. Chance." Clearly, this is not a correct description from a scientific point of view. However, it is hard to believe that the student intended the expression to be taken literally. Rather, it seems likely that the student chose this description as a didactic strategy in an attempt to harmonize the explanation with the expected cognitive level of the intended audience, which was explicitly specified to be "a small child that is not familiar with the appropriate scientific terminology" in the open-ended test item instruction. Although this type of ambiguity was only rarely encountered in the data, it is possible that such an open-ended item could stimulate a response that gives a better indication of students' understanding if the instruction is adjusted to specify another audience, for example, "other students that have not taken the same course, but have a basic scientific background."

Both external representations did show some structural features of the virus capsid. Many students raised the importance of structural complementarities for the virus capsid assembly process and used various analogies for the ability of macromolecules to fit to one another. It is well-known from previous research that both images and tangible models can be beneficial to students' understanding of structure (Copolo and Hounshell, 1995; Dori and Barak, 2001; Harris *et al.*, 2009).

Are There Any Differences in Learning Outcomes between Using a Tangible Model and an Image in a Group Exercise?

Although the quantitative results did not show any differences between the groups, the qualitative analysis did reveal some areas in which the impact of using the external representations in a group exercise seemed to differ between the conditions. It appears that students in the tangible model condition developed to a higher degree an understanding of self-assembly that included facets as important conceptual parts that could be expressed in writing. After the group exercises, almost all students in this condition included at least one facet, while many students in the image condition did not. A more subtle difference was found for the complexity of students' responses. Some descriptions by students in the tangible model group provided complex responses that included as many as four different facets. In comparison with responding to propositions that each relate to one facet, being able to formulate an explanation that simultaneously includes several facets is arguably more difficult and, thus requires a deeper and more integrated level of conceptual understanding. Therefore, differences in the complexity of responses could indicate differences in depth of understanding that may not be visible in the close-ended test used here. Although the qualitative differences in the complexity of responses were tentative in this study, it might be an intriguing area for future research in the context of students' use of tangible models.

Because two very different external representations of self-assembly were used, it is possible to discuss the observed qualitative differences between students in the two conditions in terms of the properties of the representations. In this regard, it can be noted that the tangible model offers a wider set of features analogous to the properties of the molecular system being represented. For example, the subunits move in three dimensions and actually collide with one another when the container is being shaken. The image shows the progress of the assembly using arrows that indicate the addition of more subunits to the growing capsid. Therefore, time and movement are represented by a spatial separation between intermediate structures in the image, while the tangible model maps directly to time and movement. In addition, the image uses single-headed arrows to indicate the overall direction of the process. Although this may be viewed as misleading with respect to the detailed process of self-assembly, this use of arrow symbolism may also be viewed as suitable for the system while it is far from equilibrium. Consequently, although double-headed arrows would explicitly convey the facet reversibility, they could simultaneously obscure the facet differential stability. Clearly, designing static images that support learning about a dynamic process such as self-assembly is a challenge that may need additional research into students' interpretations of the various visual components of such an image.

The two facets most directly related to movement are random molecular collisions and reversibility. Taken together, these two facets account for a large part of the qualitative differences among open-ended responses between the conditions. These differences could be explained by differences in the features of the external representations, given the observation above that the representation of movement is a main distinction between the tangible model and the image. The dynamic properties of the interactive tangible model might thus make it a powerful tool for supporting students' construction of knowledge about the dynamic process of self-assembly in a group exercise. This correlates well with results by Rotbain and coworkers (2006), showing that a tangible model of DNA supported student learning about processes such as replication more than a pictorial representation depicting the same content. The model used was flexible and allowed students to manipulate the DNA strands. It was found that students revealed more improved understanding of DNA-related dynamic processes when using a tangible model. Furthermore, the literature suggests that processes that include randomness are not intuitive for students (e.g., Friedler *et al*., 1987; Odom, 1995; Chi, 2005) and that teaching about randomness can be difficult in the context of traditional instructional approaches (Odom and Kelly, 2001). Therefore, the qualitative changes observed for the tangible model condition may indicate that it could be a possible entry point for discussions about random aspects of molecular processes in general.

Although the findings reported in the present study seem to indicate some advantages of the tangible model over the image for learning about self-assembly, it is important to discuss the purpose for which an external representation is constructed (e.g., Gilbert, 2008). In the context of the current study, it is probable that the image was created mainly to support a structural understanding of how the virus is assembled, as evidenced by the inclusion of a coloring scheme to emphasize the advanced structural concept of quasi-equivalence (Figure 1A). On the other hand, the tangible model was mainly designed to visualize the dynamic properties of self-assembly (Olson *et al*., 2007a). Thus, the findings should not be interpreted in terms of the general usefulness of either the individual external representations or the types of external representations. Nevertheless, investigating any differences in students' actual engagement with the external representations during the group exercise that may arise from the representational differences is a natural next step to uncover the basis for the qualitative differences observed in this study.

Another interesting possibility is to make a comparison between different external representations of self-assembly that have been purposefully designed to be as equal as possible in their representation of randomness and movement. In static images, important characteristics such as dynamics and progressive changes of molecular processes remain hidden. Thus, one reason for any failure in successfully supporting student learning might be that two-dimensional images are often used to illustrate processes that really occur in four dimensions (i.e., three spatial dimensions and time). This could partly be countered by using animations (McClean *et al*., 2005) or interactive models (Rotbain *et al*., 2006) in place of static images. Although many cellular and molecular animations tend to show molecular processes as one-way processes that do not include randomness and reversibility, there are examples of animations that do represent these facets (e.g., Martinez, 2013). However, such animations are usually not specifically designed for teaching about self-assembly and therefore do not represent all the other relevant facets of the self-assembly process. An interesting line of future research would be to specifically design a set of animations to support student learning of the dynamic facets of self-assembly and follow this with an experimental comparison with the tangible model used in the present study.

CONCLUSIONS

This study has shown that using external representations in a group discussion can support student learning about the process of self-assembly. The qualitative differences observed between written responses from students who worked with a static image and those who worked with an interactive tangible model could probably be explained by the differences in whether and how the external representations convey the relevant aspects of the learning content. In particular, the dynamic properties of self-assembly related to movement and randomness are represented to a higher degree in the tangible model than in the image. These facets were also the ones for which the main qualitative differences between the conditions were observed. A closer investigation of the interactive-learning processes during the group exercises is needed to fully explain the results revealed in this study.

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Supplemental Material

CBE—Life Sciences Education

Host e*t al.*

Supplemental material

Closed items used in pre- and post-test

The following ten closed items were used in the pre- and post-test developed and used in the paper:

“Students’ Learning about Biomolecular Self-Assembly using Two Different External Representations”, by Gunnar E. Höst, Caroline Larsson, Arthur Olson and Lena A.E. Tibell.

The items have been sorted according to which of five dynamic facets that they target. True and False statements are indicated by (T) and (F), respectively.

<u>Random molecular collisions</u>

- The self-assembly process of virus capsids proceeds via entirely random collisions between subunits (T)
- A subunit can bind to a complex of subunits if it by coincidence happens to have the proper orientation at the collision (T)

<u>Reversibility</u>

- Sometimes a subunit dissociates from a complex of subunits or a complete capsid (T)
- The self-assembly process of a virus only proceeds in one direction, so that both correctly and incorrectly bound subunits will remain after association (F)

<u>Differential stability</u>

- One of the driving forces behind self-assembly is that the stability is higher for multimeric complexes with a higher number of subunits (T)
- It is easier for a subunit to dissociate from an almost complete capsid than from a smaller complex of subunits (F)

<u>Influence of temperature</u>

- At lower temperatures the subunits move slower and collide with less energies (T)
- The stability of the complex increases with an increasing temperature (F)

<u>Error-correction</u>

- If a subunit binds to a complex in an incorrect way it will more easily detach than if it binds in a correct way, which leads to the process being ‘self-correcting’ (T)
- Since incorrect complexes are more stable than correct complexes, the incorrect complexes will remain (F)