

# Towards tactile sensations with a hybrid manipulative to influence learning

Balthazar Potet, Nicolas Huloux, Nadine Couture

## ▶ To cite this version:

Balthazar Potet, Nicolas Huloux, Nadine Couture. Towards tactile sensations with a hybrid manipulative to influence learning. IHM'24 - 35e Conférence Internationale Francophone sur l'Interaction Humain-Machine, AFIHM; Sorbonne Université, Mar 2024, Paris, France. hal-04487275

HAL Id: hal-04487275

https://hal.science/hal-04487275

Submitted on 3 Mar 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## Towards tactile sensations with a hybrid manipulative to influence learning Sensations tactiles avec un manipulatifs hybride pour influencer l'apprentissage

BALTHAZAR POTET\*, MIRA, Aflokkat, France and Univ. Bordeaux, ESTIA-Institute of Technology, EstiaR, France NICOLAS HULOUX\*, MIRA, Aflokkat, France and Univ. Bordeaux, ESTIA-Institute of Technology, EstiaR, France NADINE COUTURE, Univ. Bordeaux, ESTIA-Institute of Technology, EstiaR, France

Manipulatives have been used since the first half of the 20th century to improve mathematics teaching in elementary and middle school classrooms. The effectiveness of both virtual and physical manipulatives has been well-studied. However, it is still unclear how a manipulative's design influences the way it is used and its efficacy. In fact, most of the existing literature points to a lack of difference between physical and virtual manipulatives in terms of learning performance. Here, we attempt to explain this phenomenon by showing that physical and virtual manipulatives differ along too many dimensions to be meaningfully compared. We also developed a haptic virtual manipulative, which we intend to use in an experiment designed to study the influence of haptic feedback on learning. Les manipulatifs sont utilisés depuis la première moitié du 20ème siècle pour faciliter l'apprentissage des mathématiques au primaire et au collège. Leur efficacité, qu'ils soient physiques ou virtuels, est le sujet de nombreuses études. Cependant, des efforts sont encore à fournir pour comprendre en quoi la conception d'un manipulatif influence la manière dont il est utilisé et donc son efficacité. De fait, très peu de différences de performances ont été observées entre les manipulatifs physiques et virtuels. Ici, nous essayons d'expliquer ce phénomène en montrant que les manipulatifs physiques et virtuels diffèrent selon trop de dimensions de conception pour être comparés directement. Nous avons aussi créé un manipulatif virtuel avec des propriétés haptiques, que nous avons l'intention d'utiliser dans une expérience afin d'étudier l'influence des retours haptiques sur l'apprentissage.

CCS Concepts: • Human-centered computing → Haptic devices.

Additional Key Words and Phrases: Touch screen, Manipulation, Learning

Mots Clés et Phrases Supplémentaires: Interaction tactile, Manipulation, Apprentissage

### Reference:

Balthazar Potet, Nicolas Huloux, and Nadine Couture. 2024. Towards tactile sensations with a hybrid manipulative to influence learning. IHM '24: Actes étendus de la 35<sup>e</sup> conférence Francophone sur l'Interaction Humain-Machine, March 25–29, 2024, Paris, France

## 1 INTRODUCTION

Learning abstract concepts is a difficult process for numerous students. Teachers have therefore put a lot of effort into the creation of pedagogical material in order to simplify the learning process. At the beginning of the 20<sup>th</sup> century, some pedagogues [15, 30] created manipulatives, objects designed to make abstract concepts concrete for children. Since then, manipulatives have been extensively used to help students learn mathematics [11, 27].

Because a large variety of manipulatives exists, there is no simple definition of what a manipulative is. However, there are two major characteristics that define them: they refer to real, *concrete* experiences [14], and they can be moved through space by students [7]. This later property sets them apart from merely pictorial representations, which can be animated but aren't interactive [33].

Cuisenaire rods, presented in Fig. 1, are a typical example of a manipulative. Introduced in 1952 by Cuisenaire, these colored wooden rods were designed to improve the arithmetic understanding of young children [15]. Each rod is assigned a numerical value relative to its length and users can model additions by lining up rods lengthwise, while

1

<sup>\*</sup>Both authors contributed equally to this research.

comparing values by lining them up widthwise. The fact that a rod of a given length can take on multiple values is useful to develop intuitions about units [17].

However, manipulatives are not necessarily physical objects. With the advent of personal computing, *virtual manipulatives* were developed as digital versions of their physical counterparts [32]. Just like regular manipulatives, they represent abstract concepts and can be moved through space, albeit a virtual rather than physical space. Freed from physical constraints, they can possess additional features. For instance, series of manipulation can be recorded and played back for later review by a teacher [14].

Paradoxically, while both real and virtual manipulatives are widely used in classrooms [3, 43] with success in various contexts [11, 12, 21], the reason for their efficacy in supporting learning is still not fully understood [27]. Recent findings from the point of view of embodied and embedded cognition theories have highlighted the following [36]. First, manipulatives help learner by lowering the cognitive load of a task. Second, manipulation helps learner by internalizing some sensorimotor routines that can be recalled later. However, as Pouw et al. point out, "it is not yet clear how manipulatives can be designed in such a way that these different processes are optimally supported" [36].

Here, we clarify how the design of a manipulative influences its efficacy by studying the boundary between physical and virtual manipulations. For that purpose, we first define a design space to clarify which dimensions of a manipulative's design impact its use. Then, we intend to use a haptic surface based on ultrasonic friction modulation [6], to design a virtual manipulative with the addition of haptic feedback. This would fill an as of yet unexplored part of the design space, and allow us to investigate how haptic feedback influences manipulation.

#### 2 BACKGROUND ON MANIPULATIVES

### 2.1 Advantages of using manipulatives for learning

Previous studies have highlighted the advantages of using manipulatives for learning. They can motivate students and they can facilitate learning.

2.1.1 Motivation. While student motivation is a complex topic, motivated students generally perform better in an academic context [5].

Manipulatives can provide *extrinsic* motivation to students. For instance, the point of some mathematical games is merely to sugarcoat an activity assumed to be fundamentally uninteresting to students [9] or potentially threatening to their self-esteem [16], and manipulatives can be used to create such games [31]. They can also allow students to

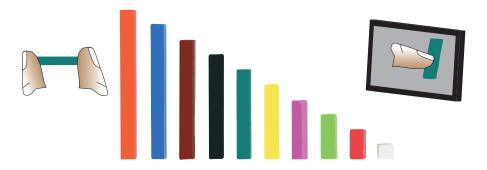


Fig. 1. Typical material of cuisenaire rods and its utilisation in their physical version (left) and virtual version (right).

relate mathematical activity to concrete everyday experience, indicating that it is an obviously useful endeavour if not necessarily valuable in itself [44].

Manipulatives can also provide *intrinsic* motivation. The idea to use specially designed objects to guide learning can be traced as far back as to at least Froebel, who designed educative *gifts* for young children in the 1830s [8]. His pedagogy was greatly influenced by the enlightenment's idea that children should be taught to think for themselves [19, pp. 20-25]. Open ended play with the toys gives the opportunity to pursue one's own goals, which is intrisically motivating.

- 2.1.2 Developmental psychology. According to Piaget's theory of cognitive development, purely symbolic thought is only available to children in the fourth and last stage of their intellectual maturation, usually attained between 11 and 15 years of age [22]. Therefore, the mathematical instruction of younger children cannot rely exclusively on symbols and they must be provided with intuition-developing sensori-motor experiences, which manipulatives can be used for [30].
- 2.1.3 Embodied cognition. According to theories of embodied cognition, thinking is an activity which happens not only in one's brain, but also in one's body and surroundings [41]. This view contradicts a more classical cognitive theory, which claims that thinking is about processing symbolic representations. This classical theory has offered the basis for a criticism of manipulatives: because concrete manipulation is fundamentally disconnected from abstract concepts, it could hinder learning [34]. The paradigm of embodied cognition makes the opposite claim: our concepts are necessarily linked to concrete experiences, which manipulatives promote [36].

In addition, from the point of view of embodied cognition, manipulatives alleviate cognitive load in some cases. They can be used to store thoughts or to perform a computation externally, thus freeing up cognitive resources for other matters [37]. For instance, a student can set some rods aside as a reminder that he will need them later.

2.1.4 Multimedia learning. The CATLM model [26] theorizes learning via audio and visual media that are possibly interactive. Recent work shows that it can be augmented to include haptic perceptual channels and still retain its explanatory power [35].

## 2.2 Physical and virtual manipulatives

A literature review found no measurable difference in efficacy between physical and virtual manipulatives [39]. Multiple studies support this conclusion, comparing virtual and physical versions of fraction blocks [10], fractions strips [28] or manipulatives specially designed to learn about the scientific method [45].

This has been supported by multiple authors that insist on the fact that an object by itself cannot promote learning and that it must be used within a clearly defined pedagogical context to help students forge meaningful concepts [23, 27]. They are putting an emphasis on careful lesson planning rather than on manipulative design.

Also, the way a manipulative is used has been identified has a key moderator on its efficacy: free exploration isn't nearly as conductive to learning as guided manipulation is [11].

Yet it is clear that different manipulatives lend themselves to different kinds of manipulation. For instance, 3-dimensional physical rods can be stacked, unlike 2-dimensional virtual rods. To identify which differences in a manipulative's design, if any, lead to difference in efficacy, we first attempt to clearly delineate how a manipulative's characteristics influence its use, going beyond the coarse distinction between physical and virtual. In doing so, we follow [24], which pointed out that direct comparisons of virtual and physical manipulatives can be problematic.

3

#### 3 A DESIGN SPACE FOR PHYSICAL AND VIRTUAL MANIPULATIVES

We wish to understand the specific affordances of physical and virtual manipulatives, and more broadly to investigate the ways a manipulative can be used. In order to do this, we define a design space with seven dimensions, see Fig. 2

Let us look again at the distinction between physical and virtual manipulatives, through the lens of our design space. As can be seen in Fig. 2, typical physical Cuisenaire rods differ from their virtual counterparts in more ways than one, indicating that it can be problematic to compare them one-to-one. Indeed, Manches has argued in [24] that experiments comparing physical and virtual manipulatives could be leaving aside specific affordances of physicality for the sake of comparison. Furthermore, meaningful differences in the ways a manipulative is used, such as differences in learning strategies, may not always result in measurable differences of academic performance [25].

## 4 THE DESIGN OF HAPTICRODS, A VIRTUAL HAPTIC MANIPULATIVE

We intend to study the potential impact of haptic feedback on the way a manipulative is used for learning. In turn, the way a manipulative is used has implications for its efficacy at improving learning [11, 23]. To avoid the pitfalls described in the previous section, we designed HapticRods, a virtual haptic manipulative with the same properties as a regular virtual manipulative while also being able to produce rich haptic sensations onto a user's fingertip. By design, it behaves like a regular virtual manipulative along every dimension but one: addition of haptic sensations along the perceptual channel of interest, see the green line in Fig. 2.

## 4.1 Haptic touchscreens

4.1.1 Surface haptics for HapticRods. Surface haptics are a type of haptic interfaces that produces haptic feedback directly onto one's fingertip [6]. Some have deformable surfaces to produce force feedback [42], other are based on vibrations [13] and some use friction modulation to produce tactile feedback [46]. Here, we use an ultrasonic friction modulation surface similar to the one in [4] to produce a large variety of haptic feedback. These interfaces are able to produce click sensations [29], as well as textures or bumps [38]. These interfaces work by vibrating at an ultrasonic frequency, creating a squeeze-film between the fingertip and a plate that reduces friction [46]. Hence, haptic feedback is produced by modulating the resonance frequency while one's fingertip explores the screen.

4.1.2 The use of haptic technology in education. Haptic technologies have been used to teach sensori-motor skills, such as playing the piano [18], typing on a Braille keyboard [40] or building a model plane [2]. They have also been employed in the context of distance learning to teach physics concepts [20]. We intend to use a haptic device for a rather different purpose, that is: to observe the impact of physicality in learning purely *abstract* concepts through manipulation.

## 4.2 Our manipulative: HapticRods

We implemented a virtual Cuisenaire rods app on a haptic tablet, Fig. 3. New rods can be created at will, then moved freely around the screen by drag-and-dropping them. A specific haptic feedback is associated with each rod length. The frequency of the haptic signal is inversely proportional to the length of the rod. When a rod is selected or when two rods collide, a "click"-like feedback is produced. The haptic feedback can also be disabled entirely, turning our app into a regular virtual manipulative which behaves closely to [1].

In terms of the design space defined in the previous section, our manipulative is very close to a regular virtual manipulative, by design. However, it also mobilizes the haptic channel to convey information. Two rods with significantly different length produce significantly different haptic feedback. Therefore, they can be distinguished by touch alone,

with no need for visual information. This is similar to the way physical rods can be told apart without looking, by

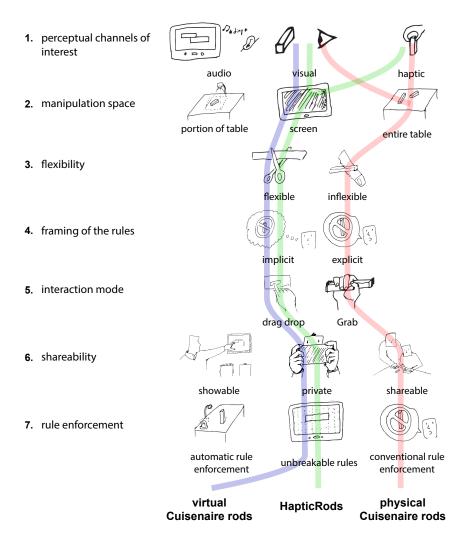


Fig. 2. The design space for Cuisenaire manipulatives along seven dimensions: 1. *Perceptual channels of interest*. We say that a perceptual channel is of *interest* when it conveys relevant information, 2. *Manipulation space*. The space in which the manipulation takes place, 3. *Flexibility*. A manipulative is said to be flexible if it can be easily modified during use, 4. *Framing of the rules*. Manipulatives are rarely meant to be used freely, except in the context of an introductory activity in order to get students acquainted with the materials, 5. *Rule enforcement*. The rules of manipulation can be enforced by convention, so that a human (either the instructor or the student themself) makes sure that the rules are provided and respected, 6. *Interaction mode*. This dimension refers to the kind of action performed by the hands using the manipulative: they manipulate either by grabbing or by drag-and-dropping, 7. *Shareability*. An entirely shareable manipulative can be manipulated by multiple persons at once, while an entirely private one can only be interacted with by a single person at a time. Paths represent a type of Cuisenaire manipulative: physical Cuisenaire rods (red) in the style of [15], virtual rods (blue) in the style of [1] and our hybrid manipulative, HapticRods (green).

guessing their lengths through grabbing. Hence, the haptic perceptual channel can be said to be *of interest* in HapticRods, just as it is in physical rods.

#### 5 CONCLUSION AND FUTURE WORKS

We presented a work in progress. We have already defined the design space for Cuisenaire manipulatives along seven dimensions, as well as the design of a new manipulative, called HapticRods, in order to experiment the advantages of using haptic manipulatives for learning.

In the very near future, we intend to show that the haptic feedback of our manipulative allows one to pay less visual attention to the screen while still performing accurately. To show this, we will task participants with solving simple fraction problems with the virtual rods. The problems will be shown on a separate screen, thus causing visual distraction for the participants. In the control condition, the haptic feedback of the app will be disabled. We will measure the average time taken to solve the tasks in both conditions. We expect haptic feedback to allow the participants to solve the tasks quickly in spite of the visual distraction. This would indicate that the visual channel is at least partially freed when haptic feedback is present. The visual channel could therefore be used to transmit additional information to the student. Or, alternatively, it could remain unused, therefore lowering the student's cognitive fatigue. A lower problem-solving time would also allow a student to go through more problems in a given time. This should allow him or her to progress more quickly.

At another level, we believe that haptics can enhance the user experience, even without visual distraction. We intend to show that the haptic click produced when a user selects a rod will reduce errors during manipulation.

The main research question to which this work contributes is whether haptic feedback leads to changes in the manipulation patterns exhibited by users. If it does, it could help with supporting the processes of embodied cognition as described in [36].

## **REFERENCES**

- [1] [n. d.]. Brainingcamp Digital Manipulatives. https://www.brainingcamp.com/cuisenaire-rods.
- [2] Richard J Adams, Daniel Klowden, and Blake Hannaford. 2001. Virtual training for a manual assembly task. *Haptics-e, The electronic journal of haptics research* (2001).



Fig. 3. An example of HapticRods on the haptic surface [4]. Rods on the bottom right can be dragged and dropped on the playground. As the user slides on the surface holding a rod, a haptic effect is played depending on which rod is selected.

- [3] Cristina Adrián-Jiménez, Noelia Jiménez-Fanjul, María José Madrid, and Cristina Pedrosa Jesús. 2022. Use of mathematical manipulatives and development of number sense in first grade primary-students. *Matemáticas, educación y sociedad* 5, 3 (2022), 10–21.
- [4] Quentin Agobert, Corentin Bernard, Balthazar Potet, and Nicolas Huloux. 2023. Eyes-Free Fingertip Guidance Based on Tactile Cues, an Extension of the Steering Law. In 2023 IEEE World Haptics Conference (WHC). IEEE. 14–19.
- [5] Eric M Anderman and Heather Dawson. 2011. Learning with motivation. Handbook of research on learning and instruction 219214 (2011).
- [6] Cagatay Basdogan, Frederic Giraud, Vincent Levesque, and Seungmoon Choi. 2020. A review of surface haptics: Enabling tactile effects on touch surfaces. *IEEE transactions on haptics* 13, 3 (2020), 450–470.
- [7] Matthew Boggan, Sallie Harper, and Anna Whitmire. 2010. Using Manipulatives to Teach Elementary Mathematics. Journal of Instructional Pedagogies 3 (2010).
- [8] Herbert Courthope Bowen. 1892. Froebel and education through self-activity. Scribner.
- [9] Amy Bruckman. 1999. Can educational be fun. In Game developers conference, Vol. 99. 75-79.
- [10] Barbara A Burns and Ellen M Hamm. 2011. A comparison of concrete and virtual manipulative use in third-and fourth-grade mathematics. School Science and Mathematics 111, 6 (2011), 256–261.
- [11] Kira J Carbonneau, Scott C Marley, and James P Selig. 2013. A meta-analysis of the efficacy of teaching mathematics with concrete manipulatives. Journal of educational psychology 105, 2 (2013), 380.
- [12] Phyllis Chinn, Greg Colyer, Martin Flashman, and Ed Migliore. 1992. Cuisenaire rods go to college. *Problems, Resources, and Issues in Mathematics Undergraduate Studies* 2, 2 (1992), 118–130.
- [13] Seungmoon Choi and Katherine J Kuchenbecker. 2012. Vibrotactile display: Perception, technology, and applications. Proc. IEEE 101, 9 (2012), 2093–2104.
- [14] Douglas H Clements. 2000. 'Concrete' manipulatives, concrete ideas. Contemporary issues in early childhood 1, 1 (2000), 45-60.
- [15] Georges Cuisenaire. 1952. Les nombres en couleurs. Nouveau procédé de calcul par la méthode active, applicable à tous les degrés de l'école primaire. Libr. Duculot-Roulin.
- [16] Derek De Holton, Afzal Ahmed, Honor Williams, and Christine Hill. 2001. On the importance of mathematical play. International Journal of Mathematical Education in Science and Technology 32, 3 (2001), 401–415.
- [17] Dianne K Erickson, Mary Kim Prichard, Nadine Bezuk, and Mally Moody. 1990. Activities: Percentages And Cuisenaire Rods. The Mathematics Teacher 83, 8 (1990), 648–654.
- [18] Likun Fang, Timo Müller, Erik Pescara, Nikola Fischer, Yiran Huang, and Michael Beigl. 2023. Investigating Passive Haptic Learning of Piano Songs Using Three Tactile Sensations of Vibration, Stroking and Tapping. Proceedings of the ACM on Interactive, Mobile, Wearable and Ubiquitous Technologies 7, 3 (2023), 1–19.
- [19] Maughn Rollins Gregory, Joanna Haynes, and Karin Murris. 2016. The Routledge international handbook of philosophy for children. Taylor & Francis.
- [20] Felix G Hamza-Lup and Ioana A Stanescu. 2010. The haptic paradigm in education: Challenges and case studies. *The Internet and Higher Education* 13, 1-2 (2010), 78–81.
- [21] Heris Hendriana, Ujang Rahmat Slamet, and Utari Sumarmo. 2014. Mathematical connection ability and self-confidence (an experiment on junior high school students through contextual teaching and learning with mathematical manipulative). International Journal of Education 8, 1 (2014), 1–11.
- [22] Bärbel Inhelder and Jean Piaget. 1958. The growth of logical thinking from childhood to adolescence: An essay on the construction of formal operational structures. Vol. 22. Psychology Press.
- [23] Constance Kamii, Barbara A Lewis, and Lynn Kirkland. 2001. Manipulatives: When are they useful? The Journal of Mathematical Behavior 20, 1 (2001), 21–31.
- [24] Andrew Manches and Claire O'malley. 2012. Tangibles for learning: a representational analysis of physical manipulation. *Personal and Ubiquitous Computing* 16 (2012), 405–419.
- [25] Andrew Manches, Claire O'Malley, and Steve Benford. 2010. The role of physical representations in solving number problems: A comparison of young children's use of physical and virtual materials. Computers & Education 54, 3 (2010), 622–640.
- [26] Richard E Mayer. 2005. Cognitive theory of multimedia learning. The Cambridge handbook of multimedia learning 41 (2005), 31-48.
- [27] Nicole McNeil and Linda Jarvin. 2007. When theories don't add up: Disentangling the manipulatives debate. Theory into practice 46, 4 (2007), 309–316.
- [28] Maria Mendiburo and Ted Hasselbring. 2014. Technology's impact on fraction learning: An experimental comparison of virtual and physical manipulatives. Journal of Computers in Mathematics and Science Teaching 33, 2 (2014), 209–231.
- [29] Jocelyn Monnoyer, Emmanuelle Diaz, Christophe Bourdin, and Michaël Wiertlewski. 2016. Ultrasonic friction modulation while pressing induces a tactile feedback. In Haptics: Perception, Devices, Control, and Applications: 10th International Conference, EuroHaptics 2016, London, UK, July 4-7, 2016, Proceedings, Part I 10. Springer, 171–179.
- [30] Maria Montessori. 2013. The montessori method. Transaction publishers.
- [31] Patricia S Moyer. 2001. Are we having fun yet? How teachers use manipulatives to teach mathematics. *Educational Studies in mathematics* 47, 2 (2001), 175–197.
- [32] Patricia S Moyer, Johnna J Bolyard, and Mark A Spikell. 2002. What are virtual manipulatives? Teaching children mathematics 8, 6 (2002), 372–377.
- [33] Patricia S Moyer-Packenham and Johnna J Bolyard. 2016. Revisiting the definition of a virtual manipulative. *International perspectives on teaching and learning mathematics with virtual manipulatives* (2016), 3–23.

- [34] Mitchell J Nathan. 2012. Rethinking formalisms in formal education. Educational Psychologist 47, 2 (2012), 125-148.
- [35] Magdalena Novak and Stephan Schwan. 2021. Does touching real objects affect learning? Educational Psychology Review 33 (2021), 637-665.
- [36] Wim TJL Pouw, Tamara Van Gog, and Fred Paas. 2014. An embedded and embodied cognition review of instructional manipulatives. *Educational Psychology Review* 26 (2014), 51–72.
- [37] Evan F Risko and Sam J Gilbert. 2016. Cognitive offloading. Trends in cognitive sciences 20, 9 (2016), 676-688.
- [38] Gabriel Robles-De-La-Torre and Vincent Hayward. 2001. Force can overcome object geometry in the perception of shape through active touch. Nature 412, 6845 (2001), 445–448.
- [39] Julie Sarama and Douglas H Clements. 2009. "Concrete" computer manipulatives in mathematics education. *Child Development Perspectives* 3, 3 (2009), 145–150.
- [40] Caitlyn Seim, John Chandler, Kayla DesPortes, Siddharth Dhingra, Miru Park, and Thad Starner. 2014. Passive haptic learning of Braille typing. In Proceedings of the 2014 ACM International Symposium on Wearable Computers. 111–118.
- [41] Lawrence Shapiro and Shannon Spaulding. 2021. Embodied Cognition. In *The Stanford Encyclopedia of Philosophy*, Edward N. Zalta (Ed.). Metaphysics Research Lab, Stanford University.
- [42] Harshal A Sonar, Aaron P Gerratt, Stéphanie P Lacour, and Jamie Paik. 2020. Closed-loop haptic feedback control using a self-sensing soft pneumatic actuator skin. Soft robotics 7, 1 (2020), 22–29.
- [43] Paul Swan and Linda Marshall. 2010. Revisiting mathematics manipulative materials. Australian Primary Mathematics Classroom 15, 2 (2010), 13–19.
- [44] Nelly Tournaki, Young Seh Bae, and Judit Kerekes. 2008. Rekenrek: A Manipulative Used to Teach Addition and Subtraction to Students with Learning Disabilities. Learning disabilities: A contemporary journal 6, 2 (2008), 41–59.
- [45] Lara M Triona and David Klahr. 2003. Point and click or grab and heft: Comparing the influence of physical and virtual instructional materials on elementary school students' ability to design experiments. Cognition and Instruction 21, 2 (2003), 149–173.
- [46] Michaël Wiertlewski, Rebecca Fenton Friesen, and J Edward Colgate. 2016. Partial squeeze film levitation modulates fingertip friction. Proceedings of the national academy of sciences 113, 33 (2016), 9210–9215.