Interactive Metabolism, a simple and robust active learning tool that improves the biochemistry knowledge of undergraduate students

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Abstract

Advances in physiology and other fields are strongly associated with a solid base knowledge of biochemistry and cell metabolism. On the other hand, the complex and abstract nature of metabolic pathways, the traditional lecture method, and other factors made the teaching-learning process of biochemistry a challenging endeavor. To overcome this, we developed and tested a novel active learning tool called Interactive Metabolism (iM-tool). The iM-tool was developed with simple and low-cost materials. We used it for interactive teaching of several metabolic pathways and physiological mechanisms for students enrolled in the Biochemistry subject belonging to different undergraduate courses. The results of evaluation tests showed that the iM-tool significantly (ANOVA, P < 0.01) and consistently improved the biochemistry knowledge of students in classrooms with up to 50 students for 7 different and consecutive academic semesters. A survey intended to mine students’ opinions on the tools showed significant satisfaction with the teaching using the iM-tool over traditional lecture-based teaching, and the iM-tool contributed to collaborative learning among students. Therefore, our results showed that the iM-tool improves the biochemistry and cell metabolism teaching-learning process in a more attractive and interactive manner.

INTRODUCTION

Cells depend on several sequences of essential biochemical reactions catalyzed by specific enzymes to extract energy from their environment as well as to use it to perform mechanical work, active transport, and synthesis of new biomolecules. This set of biochemical reactions, collectively known as metabolism, is critically important to advances in the fields of physiology, biotechnology, metabolic engineering, production of food, fuels, and drugs, as well as the discovery of novel biomarkers and drug targets, development of efficient diagnostics, and treatment protocols for different diseases (1–3). Therefore, a solid knowledge of biochemistry and cell metabolism is crucial to prepare the students enrolled in the higher undergraduate courses of health, biological, and agricultural sciences for a competitive job market (4).

All living cells have glycolysis, a canonical and highly conserved catabolic pathway that is responsible for the initial oxidation of glucose and other hexoses to pyruvate into the cytosol. Then, the pyruvate needs to be transported to mitochondria of eukaryotic cells to be completely oxidized to NADH and CO₂ through the citric acid cycle and oxidative phosphorylation. Even though glycolysis and citric acid cycle are catabolic pathways, their intermediate metabolites are also very important precursors for anabolic pathways involved in the synthesis of carbohydrates, amino acids, fatty acids, nucleotides, and other metabolites. Moreover, metabolic pathways are also regulated by important animal hormones such as insulin and glucagon (1, 2). Beyond their high complexity, connectivity, and dynamic and transient nature, all components of metabolic pathways (e.g., enzymes, intermediate metabolites, and others) also have an “invisible” nature, and therefore, they cannot be observed with a microscope or shown as a physical and touchable “thing.”

These biological features of metabolic pathways are similar to the Central Dogma concept that also has an “invisible” nature (5–7). These and other authors have reported that students have difficulties to imagine, understand, and connect complex biological phenomena that occur at the submicroscopic level (8, 9). Diverse visual representations methods such as projections, slides, figures textbooks, writing on white/chalkboard, and others have been used to make submicroscopic phenomena more understandable and “visible” for the students (8). However, several educational studies have also shown that these exposition-centered methods may negatively impact the teaching-learning process of different biology subjects, as well as the student performance and the development of important skills such as critical thinking, communication, creativity, logic, and scientific reasoning (10–16). Thus different authors have suggested the
use of alternative teaching approaches to make molecular mechanisms less “invisible.” This could help students in organizing and creating a correct and well-integrated network of metabolism, physiology, cell, and molecular biology concepts and mechanisms. Moreover, such practices create optimal learning environments to promote student engagement, stimulating the interaction among professor, students, and their classmates (5–9).

Active learning approaches improve student engagement, learning, motivation, autonomy, curiosity, interaction, attention, and performance (5, 17–20). A variety of active learning tools such as software, games, and web-based learning (15, 21–28), scientific articles (22, 29, 30), flipped jigsaw activities (16), guided practices (31, 32), problem-based learning (31, 33), and physical models (11, 34–38) have been used to improve biochemistry, cell metabolism, and physiology knowledge of students in a small, medium, and large-group classroom setting.

Physical models are a potential teaching tool to make a biological phenomenon more “visible” and less abstract, assisting professors and students in overcoming the challenges associated with the teaching-learning process of different molecular concepts and mechanisms (5, 9, 38). The use of physical models resulted in the improvement of learning of themes related to macromolecules, protein structure and function (35, 36, 39, 40), the central dogma of molecular biology (5), membrane potential and action potential (11), skeletal muscle physiology (37), and the demonstration of factors affecting the glomerular filtration rate (34). These and other studies also reported that the use of physical models stimulated the students to construct their knowledge as well as improve their critical thinking skills. Such methods also encouraged creativity, logic, discussion, and reasoning (11, 41).

Despite their benefits, the use of physical models for teaching and learning cell metabolism concepts is still scarcely explored. Thus we proposed the creation and implementation of a physical model of metabolic pathways called the “Interactive Metabolism tool” (iM-tool). The iM-tool is a simple tool made with inexpensive materials that can be used as an active learning approach in any biochemistry subject together with “how questions” and constructivist ideas. The iM-tool stimulated a more dynamic and interactive environment and improved the student’s knowledge of biochemistry and cell metabolism, ultimately contributing directly or indirectly to reduce the failure rates. Finally, the iM-tool was well received by students and could be a simple and low-cost alternative to traditional lectures in different undergraduate courses.

## MATERIALS AND METHODS

### Materials for the Interactive Metabolism Tool

The Interactive Metabolism tool (iM-tool) was developed to represent different pathways of primary metabolism according to standard textbook references (42, 43). The following materials were used to producing the iM-tool: 1) ruler; 2) scissors; 3) glue; 4) double-sided tape; 5) strip and circular magnets; 6) colored ethylene vinyl acetate (EVA) sheets; 7) white A4 sheets; 8) metal sheet (1 m²) with white background; 9) woods; and 10) computer cooler. The iM-tool systematics is described in RESULTS.

### Study Participants

The iM-tool has been used semiannually since 2016 with students enrolled in the Biochemistry subject of first-year undergraduate students in Agronomy, Bachelor of Agricultural Sciences, Veterinary Medicine, and Zootechnics at the Institute of Agricultural Sciences from Federal University of Jequitinhonha and Mucuri Valleys (UFVJM) at Unai, Minas Gerais, Brazil. Out of all students, the higher percentage of participants were women (53.36%) (Supplemental Table S2; see https://doi.org/10.6084/m9.figshare.11886357) with a range between 18 and 52 yr old (Supplemental Table S2; see https://doi.org/10.6084/m9.figshare.11886360).

The students voluntarily answered questionnaires, and all of them were informed that if they declined participation, it would not interfere with their academic performance. Moreover, all of them received feedback on their participation in the evaluation tests. All protocols for this study were approved by the Institutional Education Committee from UFVJM (Processes Identification: 011.002.2015; 033.2.001. 2017; 2018.U.2.20.047.0; 2019.U.2.20.095.0).

### Design of the Study

The main steps of this study are shown in Fig. 1. Primary metabolism pathways and physiological mechanisms were first presented and explained in traditional lectures divided into three biochemical theme sets (BTS): BTS01, Glucose Uptake by Cells, Glycolysis, Gluconeogenesis, Lactic Fermentation, and Cori Cycle; BTS02, Citric Acid Cycle, Mitochondrial Electron Transport Chain and Syntheses of ATP (Oxidative Phosphorylation); and BTS03, Photophosphorylation, Calvin Cycle, and C4 Metabolism. All these themes related to metabolism and other biochemistry basics must be covered within the semester in a maximum of 60 h, distributed in two encounters of 2 h each.

In this study, the traditional lectures were characterized by continuous use of exposition-centered methods such as chalk, chalkboards, pencil, whiteboards, data-show for the projection of images, and texts with little student participation. This definition of traditional lecturing has been used in previous works (19, 44). After each set of traditional lectures, the iM-tool was used in review lectures to improve knowledge on each BTS (Fig. 1). Therefore, we conducted three review lectures using the iM-tool in each semester. Both traditional lectures and review lectures using the iM-tool (Fig. 1) were conducted by the same professor during all of the study.

### Evaluation of the iM-Tool

We prepared two tests with 10 similar multiple-choice questions about each BTS, with different choice sequences and arrangement of items. All questions were created from the contents of the standard textbook references (42, 43) adopted in the biochemistry subject. Overall, the questions were about a specific enzyme or metabolic intermediate (e.g., “The oxidation of any monosaccharide converges to which of the intermediates in the preparatory phase of glycolysis?”), a specific metabolic pathway (e.g., “Which of the
Use of distributed among the students before (Pre) and after (Post) the review lecture lasted up to 2 h; the Pre-
answered distinct Pre-
sion, and Post-
or others (e.g., “What is the final electron acceptor of the mitochondrial electron transport chain?”). Moreover, the same level of difficulty of questions was ensured in both tests. See Supplemental Methods (see https://doi.org/10.6084/m9.figshare.13803893) to obtain more details about the level of difficulty of questions.

In each review lecture, the two tests were randomly distributed among the students before (Pre) and after (Post) the use of iM-tool (Pre-iM and Post-iM) in a way that all of them answered distinct Pre-iM and Post-iM tests (Fig. 1). Each review lecture lasted up to 2 h; the Pre-iM tests, iM-tool session, and Post-iM tests were applied on the same day. The Pre-iM test was applied 10–15 min before the beginning of the iM-tool session, which lasted 90–100 min. In the final 10–15 min, the Post-iM test was applied (Fig. 1).

All evaluation tests were analyzed, and the total number of correct answers was used to calculate the percentage score and obtain the student performance in the tests. Then, we compared the percent score between Pre-iM and Post-iM tests to evaluate whether the iM-tool improved the student’s knowledge of metabolic pathways and physiological mechanisms.

Student Feedback about iM-tool

The student feedback about the iM-tool was obtained at the end of the corresponding semester (Fig. 1). For this, the students answered a questionnaire containing 16 multiple-choice questions about the iM-tool. The alternatives of 13 questions followed the Likert scale ranging from 1 to 5: 1) strongly disagree; 2) disagree; 3) neither agree nor disagree (neutral); 4) agree; and 5) strongly agree (Table 1). However, three of the questions presented different alternatives (Supplemental Table S3; see https://doi.org/10.6084/m9.figshare.11886369). We also included an optional free space for students to describe the positive and negative aspects of the iM-tool.

Statistical Analysis and Data Visualization

Our study was conducted for seven consecutive academic semesters (Year-Semester: 2016-01, 2016-02, 2017-01, 2017-02, 2018-01, 2018-02, and 2019-01). In total, we performed 21 review lectures with iM-tool, 3 by semester (Fig. 1). However, Pre-iM and Post-iM tests used in the semesters 2016-01, 2016-02, and 2017-01 were identical and the number of students that participated was lower than in the next semesters. Thus we used the data obtained through Pre-iM and Post-iM tests applied among the semesters 2017-02 and 2019-01 for the iM-tool evaluation.

We used standardized questionnaires since the second semester of 2017 to obtain student feedback about the iM-tool. In previous semesters, this questionnaire was not complete and standardized. Thus we also used the data obtained from the semesters 2017-02 and 2019-01 to analyze the student feedback about iM-tool.

One- and two-way ANOVA were used to determine statistical differences in Pre-iM and Post-iM tests. The homogeneity of variance was checked by Levene’s test and Bartlett’s test, and the Shapiro-Wilk’s test was used to check data adjustment to normality. Some data in RESULTS are presented as means ± SD. The total number of students that participated in this study varied by semester and review lectures, but it is indicated in the tables, figures, legends, and RESULTS.

Pearson’s chi-square test was used to test the association between questions and alternatives of the student feedback (questionnaires) about iM-tool. When a significant relationship was found among variables, we further examined the standardized Pearson residuals to identify the most contributing cells in the contingency table to the total chi-square score (45).

All statistical analyses and data visualization were performed using R (version 3.5.0) (46). The R stats package (46) was used for ANOVA, Bartlett’s test, Shapiro-Wilk’s test, and
chi-square test, while the R car package (47) was used for Levene’s test. Boxplots were generated with R ggplot2 (48) and ggpubr (49) packages. Balloon plots were used to represent the relative magnitude of the corresponding component into student feedback data and were generated with R gplots package (50). Standardized Pearson residuals were shown by balloon plots using R corrplot package (51).

## RESULTS

### Development and Operation of the Interactive Metabolism Tool

The learning tool proposed in this work consisted of a metal sheet fixed on a wooden plank (Fig. 2A and B), on which primary metabolism pathways can be assembled by professor and students using pieces of colored EVA attached to a magnet (Fig. 2C). EVA pieces were identified to represent the components of the cell and pathways such as intermediate metabolites, enzymes, membranes, receptors, transmembrane transporters, the direction of enzymatic reactions, ATP, ADP, P, , NADH, FAD, FADH2, NADPH, CO2, O2, H2O, and H. Moreover, tissue cells (e.g., muscle, hepatic, and pancreatic tissues) and intracellular compartment (cytosol, mitochondria, and chloroplast) can also be represented simultaneously on the same metal sheet depending on the pathways and physiological mechanism that are being addressed. As the EVA pieces of this tool are movable, the professor and students can together and interactively assemble any metabolic pathway on the metal sheet. Therefore, we named this tool “Interactive Metabolism” (iM-tool).

To improve and fix the student knowledge on biochemical themes, we used the iM-tool, as described above, in review lectures after traditional lectures (Fig. 1). To make this, all iM-tool components, metal sheet, and identified EVA pieces were placed on the table in front of all the students, and then the professor asked “how” questions about a specific pathway and physiological mechanism. When the students answered the questions, the EVA pieces were placed on the metal sheet to assemble the pathway. At the same time, questions made by students were answered by the professor or by the classmates themselves. Thus, important metabolic pathways and physiological mechanisms such as glucose uptake by muscle and hepatic cells induced by insulin, glycolysis, gluconeogenesis, lactic fermentation into myocyte cells under low oxygen concentration, Cori cycle, production of acetyl-CoA, citric acid cycle, mitochondrial electron transport chain, syntheses of ATP (oxidative phosphorylation), photophosphorylation, Calvin cycle, biosynthesis of sucrose and starch, C4 metabolism, and alcoholic fermentation (Fig. 2, D-G, and Supplemental Figs. S1 and S2, respectively: see https://doi.org/10.6084/m9.figshare.11886381 and https://doi.org/10.6084/m9.figshare.11886351) were interactively assembled by the professor and students in review lectures.

### Implementing the iM-tool

In total, the iM-tool was presented and applied to 378 students enrolled in the Biochemistry subject for at least four semesters (2017-02, 2018-01, 2018-02, and, 2019-01). There were two classes per semester each one with 40 to 50 students. Undergraduate students of distinct courses participated: Agronomy (19.58%), Bachelor of Agricultural Sciences (49.74%), Veterinary Medicine (26.98%), and Zootechnics (3.70%) (Supplemental Table S4; see https://doi.org/10.6084/m9.figshare.11886381 and https://doi.org/10.6084/m9.figshare.11886351). These data indicate that in the same biochemistry class there were students with very diverse backgrounds, who also had different course goals. Despite that, the tests were the same as well as all revisions lectures were conducted by the professor in the same way.

### Evaluation of the iM-tool

To evaluate the iM-tool, we applied multiple-choice tests about three biochemical theme sets before (Pre-iM) and after (Post-iM) using the iM-tool in review lectures (Fig. 1). Thus we hypothesized that whether the tool had a positive effect on biochemistry learning, the score mean obtained by students in the Post-iM tests would be higher than in the Pre-iM tests. Similar evaluation methods using Pre- and Post-tests have been used in previous work (11, 16, 52, 53).

Table 1. The questionnaire used to get the student feedback about iM-tool

| Question ID | Question |
|-------------|----------|
| Q01 | The use of the iM-tool was interesting for the biochemistry teaching-learning process. |
| Q02 | The iM-tool is more interesting for the biochemistry teaching-learning process than traditional lectures. |
| Q03 | Even though the iM-tool has been interesting, I still prefer the traditional lectures. |
| Q04 | The iM-tool allows the best interaction of the student with the biochemical themes. |
| Q05 | The use of the iM-tool in the teaching-learning process becomes the student a protagonist in the construction of their knowledge and puts the professor as a mediator. |
| Q06 | The use of the iM-tool in the biochemistry teaching-learning process stimulates the students’ integration and participation. |
| Q07 | The biochemistry teaching-learning process using the iM-tool requires prior knowledge. |
| Q08 | It was possible to understand the functioning of the Glycolysis and Gluconeogenesis pathways only with the traditional lectures. |
| Q09 | The use of the iM-tool helped me to better understand the functioning of the Glycolysis and Gluconeogenesis pathways. |
| Q10 | It was possible to understand the functioning of the Citric Acid Cycle, Mitochondrial Electron Transport Chain, and Syntheses of ATP (Oxidative Phosphorylation) pathways only with the traditional lectures. |
| Q11 | The use of the iM-tool helped me to better understand the functioning of the Citric Acid Cycle, Electron Transport Chain, and Syntheses of ATP (Oxidative Phosphorylation) pathways. |
| Q12 | It was possible to understand the functioning of the Photophosphorylation, Calvin Cycle, and C4 Metabolism pathways only with the traditional lectures. |
| Q13 | The use of the iM-tool helped me to better understand the functioning of the Photophosphorylation, Calvin Cycle, and C4 Metabolism pathways. |

IM-tool, Interactive Metabolism tool. The questions alternatives followed the Likert scale as explained in MATERIALS AND METHODS.
Two-way ANOVA showed that both tests (Pre-iM and Post-iM) and semesters were significantly ($P < 0.001$) associated with different student scores and might interact to create a synergistic effect. However, the interaction between tests and semesters was not significant ($P > 0.05$), which indicates that the relationships between tests and student scores do not depend on the semester.

The mean scores obtained by students on Post-iM tests about Glucose Uptake, Glycolysis, Gluconeogenesis, Lactic Fermentation, and Cori Cycle (Fig. 3A), Citric Acid Cycle, Mitochondrial Electron Transport Chain, and Syntheses of ATP (Oxidative Phosphorylation) (Fig. 3B), Photophosphorylation, Calvin Cycle, and C₄ Metabolism (Fig. 3C) were significantly ($P < 0.01, P < 0.001$, and $P < 0.0001$) higher than mean scores of Pre-iM tests by four different and consecutive academic semesters (2017-02, 2018-01, 2018-02, and 2019-01) (Fig. 3). When we consider all the tests scores from these four semesters together ($n = 938$ Pre-iM and $n = 938$ Post-iM tests) to obtain a global mean, we could see that the mean student scores on Pre-iM tests increased from $46.42\%$ (SD $\pm 3.18$) to $62.00\%$ (SD $\pm 1.29$) on Post-iM tests, a robust and significant ($P < 0.05$) increase of $15.58\%$. Similar results were observed when the iM-tool was applied on 2016-01, 2016-02, and 2017-01 semesters (Supplemental Fig. S3; see https://doi.org/10.6084/m9.figshare.11886354). However, in these semesters, the multiple-choice questions of Pre-iM and Post-iM tests were identical and the number of students was lower than in the following semesters. Moreover, in those semesters (2016-01 to 2017-01), the EVA pieces were very small and their identification, colors, and shape were not well standardized. Gradually, all these topics were improved over those semesters.

If the iM-tool improved the students’ knowledge about biochemistry, we supposed that the pass rate of this subject...
would also be improved. Therefore, we compared the pass rate of the semesters before using the IM-tool with those that made use of it. Indeed, the pass rate of biochemistry subjects increased by ~17% after the creation and implementation of the IM-tool. Taken together, these results show that the Interactive Metabolism tool is robust for improving student knowledge about primary metabolic pathways in microorganisms, animals, and plants. Furthermore, the IM-tool also contributed directly or indirectly to reduce the failure rate in the biochemistry subject.

**Student Feedback about IM-Tool**

At the end of each semester, a questionnaire was applied to obtain the student feedback about IM-tool (Fig. 1 and Table 1 and Supplemental Table S3). The student responses obtained by four academic semesters (2017-02, 2018-01, 2018-02, and 2019-01) were summed up in a single set of data. Analysis of this absolute data revealed that the student answers frequency varies among questions and alternatives (Fig. 4A). Moreover, chi-squared analysis indicates a strong and significant [χ² (Ref. 46) = 1913.6, P < 0.0001] association among the students’ answer frequency and alternatives. However, these analyses provide little information about the nature or strength of these associations (45). To overcome this, we used the standardized Pearson residuals (SPR) analyses to identify those specific cells making the greatest contribution to the chi-square test result. An SPR that exceeds 2 in absolute value above or below zero indicates, respectively, a positive or negative dependence between cells in a contingency table (45). Thus according to the residue values, a positive or negative association can be indicated between each answer frequency and alternatives (Fig. 4B).

Through SPR analyses we found a positive and significant correlation among the frequencies of students that strongly agreed that the use of the IM-tool was interesting for the teaching-learning process of biochemistry (Fig. 4B, Question ID: SQ01) and more interesting than traditional lectures (Fig. 4B, SQ02). Moreover, most of the students strongly disagree or disagree with the statement that they still prefer traditional lectures despite the IM-tool had been interesting, revealing that the IM-tool was an interesting alternative (Fig. 4B, SQ03).

The students strongly agreed that the IM-tool allows better interaction with biochemistry themes (Fig. 4B, SQ04) and stimulates their integration and participation during the teaching-learning process (Fig. 4B, SQ05). All students believed that the IM-tool allowed better memorization and assimilation of the theoretical content (Supplemental Fig. S4A, Question ID: SQ01; see https://doi.org/10.6084/m9.figshare.13820705), and they strongly agreed that the biochemistry teaching-learning process using the IM-tool requires prior knowledge (Fig. 4B, SQ07). Furthermore, the students were very satisfied with the use of IM-tool in biochemistry teaching (Supplemental Fig. S4, B and C, SQ02). On the other hand, the student satisfaction level with the presentation form (size, colors, and objects) of the IM-tool was positively correlated with the alternatives.

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**Figure 3.** Evaluation of Interactive Metabolism Tool (IM-tool). The IM-tool improves the students’ knowledge about biochemistry themes, such as Glucose Uptake, Glycolysis, Gluconeogenesis, Lactic Fermentation, and Cori Cycle (A); Citric Acid Cycle, Mitochondrial Electron Transport Chain, and Syntheses of ATP (Oxidative Phosphorylation) (B); and Photophosphorylation, Calvin Cycle, and C₄ Metabolism (C). The data represent the percent score obtained by each student in tests applied Pre and Post use of the IM-tool in different semesters (see Fig. 1 and MATERIALS AND METHODS for more details). All the data obtained from Pre-M and Post-M Tests were expressed in the notched box plot. Box line limits indicate the 25th and 75th percentiles; the box-plot center line shows the median (i.e., 50th percentile); whiskers extend to 5th and 95th percentiles. Outliers are represented by black squares. Asterisks represent the sample mean. Individual data points are represented by open circles, and sample size (n) is indicated below the minimum whisker or outlier. Significant differences were determined by one-way ANOVA and are denoted by different P values at top. Means significantly different are indicated by **P < 0.01, ***P < 0.001 and ****P < 0.0001.
unsatisfied, impartial, and satisfied (Supplemental Fig. S4, B and C, SQ03).

Most students disagreed or neither agreed nor disagreed (neutral) that was possible to understand the functioning of the Glycolysis, Gluconeogenesis (Fig. 4B, Q08), Citric Acid Cycle, Mitochondrial Electron Transport Chain, Syntheses of ATP (Oxidative Phosphorylation) (Fig. 4B, Q10), Photophosphorylation, Calvin Cycle, and C4 Metabolism pathways with the traditional lectures only (Fig. 4B, Q12). However, the students agreed or strongly agreed that the use of the iM-tool assisted in a better understanding of the functioning of all before mentioned pathways (Fig. 4B, Q09, Q11, and Q13). Taken together, these surveys show that the iM-tool was well evaluated and accepted by students and that they would rather learn biochemistry through iM-tool than the traditional lectures.

**DISCUSSION**

We have been teaching biochemistry and cell metabolism for 80 to 100 students of undergraduate courses in Agronomy, Bachelor of Agricultural Sciences, Veterinary Medicine, and Zootechnics (Supplemental Table S4). These students normally have very diverse backgrounds and different goals to reach during their courses, and most of them do not have enough knowledge in organic chemistry. Moreover, all biochemistry and cell metabolism concepts have an “invisible” and dynamic nature, high complexity level that requires an understanding of integration, organization, and regulation, making the learning process more difficult and demanding more time for studying. This is even more aggravated based on the fact that we must cover all these themes in 15 wk, with 4 h/wk at maximum, divided into two periods of 2 h each.

Following prior instructors and professors, we also started using only traditional lectures to teaching biochemistry and cell metabolism. However, for different reasons, this teaching approach has already been shown to be relatively ineffective for student learning (10, 12, 13, 15, 16). Indeed, after some time we also observed that only traditional lectures were not enough to achieve student engagement and satisfactory learning gains. Therefore, we always have faced a very challenging pedagogical context, in which the classroom is composed of a relatively high number of very different students that need to understand how the cell metabolism works with limited time and resources.

In that context, we asked ourselves how to teach cell metabolism, since subjects in that area are usually large, complex, and abstract, without losing quality and motivation and performance of students. Moreover, how to do all of it using the limited time available, using very limited financial resources, and doing so in a nonconventional manner. The employment of learning techniques that encourage and assist students to visualize what is going on inside a cell might be very useful to answer these questions (9). Thus we hypothesized that the use of a physical model of different metabolic pathways would be especially helpful for undergraduate students to learn more than lecture-based methods, as this active-learning tool provides resources that allow the students to see, touch, manipulate, and build the metabolic pathways during any biochemistry lecture.

**Figure 4.** Student feedback about the Interactive Metabolism Tool (iM-tool). The iM-tool was well accepted by biochemistry students, and they preferred it instead of the traditional lectures. A: balloon plot shows the frequency of student answers per question and alternatives about iM-tool. Each cell (square) contains a circle whose diameter corresponds to the number of student answers. The question descriptions can be seen in Table 1 using the Question ID. Alternatives: SD, strongly disagree; D, disagree; N, neither agree nor disagree (neutral); A, agree; SA, strongly agree. B: colored balloon plot shows the standardized residuals of the Pearson chi-square analysis for the number of student answers per question and alternatives shown in A. The circle diameter is proportional to the amount of the cell contribution to the total Chi square score, while the scale color is associated with negative and positive residuals represent, respectively, a significantly negative (red, greater than −2.0) or positive (blue, <2.0) correlation between the corresponding question and alternative. The total number of students (n = 253) was counted at the end of 4 academic semesters (2017-02, 2018-01, 2018-02, and 2019-01).

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**Table 1.** The survey conducted to evaluate the students’ satisfaction with the iM-tool. The alternatives shown in question 01 have been removed from the residual analysis since they were not used in any alternative. Question ID: A, agree; SA, strongly agree; D, disagree; N, neither agree nor disagree (neutral); SD, strongly disagree. The total number of students (n = 253) was counted at the end of 4 academic semesters (2017-02, 2018-01, 2018-02, and 2019-01).

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**Table 2.** Comparison between total Chi square scores of analysis for number of student answers per question and alternatives in A and B. The student feedback showed that the learning with the iM-tool was more effective than traditional lectures. A: balloon plot shows the frequency of student answers per question and alternatives about iM-tool. B: colored balloon plot shows the standardized residuals of the Pearson chi-square analysis for the number of student answers per question and alternatives shown in A. The circle diameter is proportional to the amount of the cell contribution to the total Chi square score, while the scale color is associated with negative and positive residuals represent, respectively, a significantly negative (red, greater than −2.0) or positive (blue, <2.0) correlation between the corresponding question and alternative. The total number of students (n = 253) was counted at the end of 4 academic semesters (2017-02, 2018-01, 2018-02, and 2019-01).
**iM-Tool** is a Simple and Low-Cost Alternative to Be Used in Different Undergraduate Courses

In this report, we presented the Interactive Metabolism tool (iM-tool) as a simple physical model and didactic approach to improving student performance in the Biochemistry course in different undergraduate majors. The iM-tool consisted of a metal sheet on which metabolic pathways, represented by identified pieces of colored EVA attached to a magnet (Fig. 2, A–C), can be assembled by the professor and students interacting with each other.

A few studies reported that the low availability of financial resources and other reasons have been a challenge to adopt active learning approaches instead of traditional lectures (17, 54, 55). On the other hand, we developed iM-tool using low-cost materials that can be easily found in local stores. In total, we spend about US$50.00 (Brazil, R$250.00) to acquire all the materials. Moreover, because of its simplicity, the iM-tool can be easily built by anyone and used immediately by professors and students in their lectures. Therefore, the iM-tool could also be an alternative to be used in places with limited financial resources.

The iM-tool was presented to two classes per semester each one with 40 to 50 students from 4 undergraduate courses in agricultural sciences (Supplemental Tables S1, S2, and S4). Although these students had different backgrounds and goals on their majors, the iM-tool had a positive effect on the student’s biochemistry knowledge (Fig. 3 and Supplemental Fig. S3). These results are supported by a previous study that shows that active learning approaches also had a positive impact on courses with <50 students across Science, Technology, Engineering, and Math (STEM) disciplines (19). Their study along with our results suggests that the iM-tool could be easily adapted to a variety of subjects and widely used with students from other higher undergraduate courses such as Medicine, Nursing, Physical Education, Pharmacy, Nutrition, and Dentistry.

**iM-Tool Limitations and Possible Solutions**

The student’s satisfaction level with the presentation form (size, colors, objects) of the iM-tool was positively correlated with the alternatives “unsatisfied,” “impartial,” and “satisfied” (Supplemental Fig. S4, B and C, SQ03). This result could possibly be related to class size. Different studies have shown that active learning and physical model-based activities are beneficial in small classes (19, 35). In this work, there were a maximum of 50 students in each class, and there might have been some who had difficulty seeing the EVA pieces on the metal sheet because of the distance within the classroom. Thus the class size (space dimensions of classroom and number of students) is probably the main limitation of the use of the iM-tool. Because of this, we believe that the implementation of iM-tool in a class with a relatively small number of students could cause greater learning gains. Another alternative would be to divide students into small groups who could manipulate the iM-tool under the professor’s guidance. However, both alternatives may require more financial, human, and physical resources.

**iM-Tool and “How” Questions**

Educational works have shown that the question “How does it work?” does not automatically occur to students (9).

Thus, as suggested by these authors, we explicitly and simultaneously used “how” questions and the iM-tool to gradually introduce the students to broader metabolic and physiological contexts such as how the cells extract energy from glucose; how the glucose can be absorbed by muscle and hepatic cells in insulin-dependent way (Supplemental Fig. S1A); how the glucose can be completely oxidized to CO2 and H2O (Fig. 2, D–F); how the energy from glucose oxidation can be used for the synthesis of ATP through oxidative phosphorylation (Fig. 2, F–G); how myocyte cells and yeast respond to the low oxygen concentration, respectively, by production of lactate (Supplemental Fig. S1C) and ethanol (Supplemental Fig. S1F); how the liver and muscle are connected by the Cori cycle (Supplemental Fig. S1D) for recovering the lactate and use them for biosynthesis of glucose through gluconeogenesis (Supplemental Fig. S1B); and how some cells can use photons and molecules of low energetic level (CO2 and H2O) to synthesis of glucose, sucrose, and starch (Supplemental Fig. S2), which could be subsequently oxidized in animal, plant, and microorganism cells.

An active learning strategy similar to iM-tool has also been used specifically for the teaching of membrane potential and action potential (11). Here, the iM-tool was used in a broader sense for teaching and learning important metabolic pathways and other physiological mechanisms (Fig. 2, D–G and Supplemental Figs. S1 and S2). Finally, our results are supported by previous studies that demonstrated that through the construction of two- and three-dimensional (3-D) physical models of amino acids, proteins, biomolecules, and molecular processes, the students and their peers can “see” molecular mechanisms and learn new things and possibilities (5–8, 35).

**iM-Tool Is an Active Learning Approach, Is an Alternative to Traditional Lectures, and Was Well Accepted by Students**

The iM-tool caused a positive effect on the student’s biochemistry knowledge (Fig. 3 and Supplemental Fig. S3). However, would this result be achieved without using the iM-tool? Could the learning gains also be achieved using only a pencil and whiteboard, as an expository lecture? Previous educational research (5, 19) and our data of pass rate in biochemistry indicate that the rate increased ~17% after the implementation of the iM-tool.

Together, iM-tool and our instructional approach created an environment within the classroom that stimulated the engagement, interaction, and discussion among the students as well as put them as the protagonists in the construction of their biochemistry knowledge (Fig. 4, A and B, QO4-06). A meta-analysis established that “Active learning strategies engage students in the process of learning through activities and/or discussion in class, as opposed to passively listening to an expert” (19). Therefore, this study and our results indicated that the iM-tool is an active learning tool because professor and students can discuss, understand, and interactively assemble the different primary metabolic pathways common to microorganisms, animals, and plants on the metal sheet during a lecture (Fig. 2 and Supplemental Figs. S1 and S2).

Extensive research supports that the use of active learning tools improves a student’s performance across all subjects,

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**INTERACTIVE METABOLISM TOOL (IM-TOOL)**
class size (i.e., number of students), course types, and course levels more than expository lectures or nonphysical-model-based activities (5, 19). Here, our survey opinion results showed that most students are very satisfied with the use of iM-tool in biochemistry teaching and that it was well accepted by them. They also preferred the use of iM-tool rather than the traditional lectures (Fig. 4, A and B, Q01-03; Supplemental Fig. S4, B and C, SQ02). The students also believe that the iM-tool allowed a better understanding and assimilation of the biochemical content and how catabolic and anabolic pathways work (Fig. 4B, Q09, Q11, and Q13; Supplemental Fig. S4A, SQ01). The students strongly agreed that the biochemistry teaching-learning process using the iM-tool requires prior knowledge (Fig. 4B, Q07). Moreover, most students disagreed or neither agreed nor disagreed (neutral) that it was possible to understand how many metabolic pathways work only with the traditional lectures (Fig. 4B, Q8, Q10, and Q12). All these results are also supported by previous studies (5, 11, 13, 41).

iM-Tool is Aligned with Constructivist Ideas

The professors have an important role in the teaching-learning process when using active learning tools because they must encourage the discussion among students about the main topic through listening and providing constructive feedback or eliciting more in-depth responses through probing questions (17, 41). As in other work with active learning (29), during the review lecture using iM-tool, the professor helped the students search for answers to the questions, encouraged creativity, and intervened when there was no clarity on the topic. Moreover, during the iM-session, the students were also encouraged to discuss and answer questions with their classmates and they were instructed to not allow the discussions to proceed until everyone understood how to solve the questions (29).

Active learning resources encourage and promote social skills, sharing of doubts and difficulties, exchanging of information, and collaborative construction of knowledge (17, 29, 41). Indeed, our survey showed that the iM-tool stimulated the interaction and discussion among the students as well as put them as the protagonists in the construction of their biochemistry knowledge (Fig. 4, A and B, Q04-06). Therefore, our results and analyses indicate that the iM-tool is aligned with constructivist ideas and that the iM-tool approach would help decrease the focus on what professors are doing (i.e., lecture-centered mode) and would increase the possibilities for students to construct their knowledge through more active than passive learning strategies (56–59).

Finally, we asked a team of students to present a seminar about evidence that the Entner-Doudoroff pathway of glucose degradation operates in cyanobacteria and plants (60). We expected them to use only exposition methods such as slide-shows with text and figures. However, they used the iM-tool to complement their seminar presentation about this complex theme (Supplemental Fig. S5; see https://doi.org/10.6084/m9.figshare.12776864). Because of this, we supposed that iM-tool had other positive effects on students. Maybe it inspired them to use active learning tools in their academic activities such as seminar presentations. Thus this is evidence that the iM-tool stimulated student creativity.

iM-Tool Improves the Student’s Knowledge about Biochemistry

Although our results have shown that the iM-tool was well evaluated by students (Supplemental Fig. S4), did this tool improved their knowledge about biochemistry theme sets? To answer this question, we have been used a pretest-posttest design (52). Hereby, we demonstrated that the iM-tool increased significantly the student knowledge about primary metabolic pathways and physiological mechanisms of animals, plants, and microorganisms (Fig. 3; Supplemental Fig. S3). We know that a strict experimental design requires the use of a control group that does not receive intervention and others that receive it. However, in this work, we encountered several limitations such as institutional legislation and another one that did not allow differential treatment for the students. Thus we used the Pre-iM and Post-iM test design (Fig. 1). Moreover, the pretest-posttest designs are common, adequate, and well accepted in educational research (52) and have been widely used to analyze and evaluate the effects of new and innovative educational approaches in student learning (5, 11, 16, 53, 61–64). The score mean obtained by students in the Pre-iM tests suggests that learning gains would not be obtained using only teaching expository methods (Fig. 3; Supplemental Fig. S3). On the other hand, more studies are necessary to confirm if similar learning gains would be obtained with or without the iM-tool use. Although we did not use a control group, the literature and our results allow us to conclude that the iM-tool was very effective in improving the student’s knowledge in biochemistry.

The overall mean student scores on Post-iM tests increased 15.58% after using the iM-tool. Moreover, the pass rate of whole biochemistry subject increased by ~17% after the creation and implementation of the iM-tool. Similar learning gains were obtained when 3-D printed models were used to facilitate the learning of protein structure-function relationships in Biochemistry courses (35). Moreover, a similar reduction in failure rates was observed across STEM disciplines that used active learning activities (19). Together, these results indicate that the iM-tool directly or indirectly contributed to increasing the pass rate in the biochemistry subject.

Future Studies and Perspectives

We did not compare iM-tool with any other nontraditional educational approach or expository methods, because we used pretest-postest designs to evaluate the iM-tool (Fig. 1 and Fig. 3). Therefore, it is unclear whether the iM-tool is better or worse than other educational nonmodel-based activities such as the use of software, games and web-based learning (15, 21–28), scientific articles (22, 29, 30), flipped jigsaw activity (16), guided practices (31, 32), peer discussion, and problem-based learning (31, 33). Newman et al (5) have already demonstrated that students exposed to physical model-based activities (similar to iM-tool) had higher learning gains on Central Dogma concepts than those exposed to other nonmodel-based activities. Nevertheless, more studies are necessary to verify the iM-tool performance in comparison with other nontraditional educational approaches. On the other hand, we believed that iM-tool can be used as a supplementary tool in the lectures.
Our results demonstrated that the iM-tool improved the students’ knowledge about cell metabolism and that it was well accepted by most of them. Thus could iM-tool completely replace traditional lectures based on exposition methods? Maybe this would be possible (14). However, we suggest that iM-tool and lecture-based methods be used together so that one complements the other approach. For example, phenotype mutants and biological data are very important in understanding the cell metabolism and several physiological mechanisms, but it is very difficult to represent this information through iM-tool. In this case, the slideshow would be more appropriate. Indirectly, our volunteer students have already demonstrated this (Supplemental Fig. S5). Therefore, more studies are also necessary to know whether traditional lectures based on the only exposition methods could be completely replaced by the iM-tool.

Conclusions

We developed a new, robust, and well-accepted active learning tool to improve the student’s knowledge of biochemistry. Our results demonstrated that the iM-tool was useful and positively contributed to the teaching-learning processes, the performance and engagement of the students, and the development of skills necessary for the broad and integrated understanding of Biochemistry and Physiology. Additionally, the students had a positive perception of iM-tool, and our results also indicated that through this new approach, we created an active learning environment in the class. Thus we will expand the iM-tool through the inclusion of other catabolic and anabolic pathways. Finally, we believe that the iM-tool will be an inspiration for professors who wish to break away from the traditional lecture model and contribute to the advancement of the basic and applied sciences.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

W.F.C. conceived and designed research; V.C.P.L.A.d.F. and W.F.C. performed experiments; W.F.C. analyzed data; V.C.P.L.A.d.F. and W.F.C. interpreted results of experiments; W.F.C. prepared figures; W.F.C. drafted manuscript; W.F.C. edited and revised manuscript; W.F.C. approved final version of manuscript.

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