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Novel study guides for biochemistry meaningful learning in biology: a design-based research

Estudos dirigidos inovadores para a aprendizagem significativa de bioquímica no curso de biologia: uma pesquisa baseada em design

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Abstract

To address the usually decontextualized transmission of information in biochemistry teaching, three interventions in a discipline (Metabolism) for Biology majors were applied as innovative study guides. We describe the development, application, and evaluation of two study guides, contextualized with a real problem or an integrative view, using broad themes like evolution and metabolic adaptation. In order to evaluate the impact of both interventions on interest, motivation, and learning of the metabolic pathways, a design-based research with cycles of application and assessment was carried out, by means of classroom observation, grade analysis in written exams, and students' interviews. Analysis and interpretation of the results point to benefits for teaching and learning, with helpful information to guide elaboration and refinement of new teaching materials and to make active learning more meaningful.

Keywords: Study guide; Biochemistry; Design-Based Research.

Resumo

Para lidar com a transmissão em geral descontextualizada da informação no ensino de bioquímica, foram aplicadas três intervenções na disciplina Metabolismo para Biologia, na forma de estudos dirigidos inovadores. Descrevem-se a construção, aplicação e avaliação de dois estudos dirigidos, contextualizados como um problema real ou uma visão integrativa, usando temas amplos como evolução e adaptação metabólica. A fim de avaliar o impacto de ambas as intervenções sobre o interesse, motivação e aprendizagem das vias metabólicas, foi realizada uma pesquisa baseada em design com ciclos de aplicação e avaliação, por meio de observação em sala de aula, análise de notas em provas e entrevistas com estudantes. A análise e a interpretação dos resultados indicam benefícios para o ensino e a aprendizagem, com informações úteis para orientar a elaboração e o refino de novos materiais de ensino e para tornar a aprendizagem ativa mais significativa.

Palavras-chave: Estudo dirigido; Bioquímica; Pesquisa baseada em design.

1 Introduction

The teaching and learning of Biochemistry involve a range of challenges, from the vocabulary to the high-level of abstraction needed for conceptual understanding [1]. They also demand a basic knowledge on Chemistry, a complex area in which students usually bring incomplete or mistaken concepts [2,3].

Traditional Biochemistry teaching focuses on transmission and memorization of content, in general with excessive details in a decontextualized setting. For this reason, the subject becomes unattractive since this teaching approach hampers the identification of essential concepts. In this context, students only memorize disconnected pieces of information and reproduce them in tests, soon forgetting what they have “learned”. Then, the stage is set for the discipline to be one of the most feared by life sciences’ students, as much as Calculus for the hard sciences. Therefore, Biochemistry makes indispensable the use of motivational strategies geared to each target audience, aiming at contextualizing subject so that arouse interest, prompt study, and foster learning.

Higher education has experienced a paradigm shift in relation to teaching and learning – from a professor-centered teaching (lecture-based traditional methodology) to learning processes focused on student, that breaks away passivity and promotes a more participatory attitude. This posture characterizes the so-called active learning methodologies [4,5], which pave the way for a deeper learning [6]. In this unconventional scenario, the professor’s role also changes – from an information transmitter to a guide, organizer of learning experiences.

Since the advent of Internet in mid-1990s, the so-called “digital natives” [7] are characterized by a generation of visual learners, used to increasingly sophisticated electronic devices. Although able to perform more than one task at a time, they find difficulties in maintaining focus and deepening information [8]. In this context, the professor’s role is essential for planning and didactic transposition of the biochemical content. For this purpose, it is fundamental the care with motivational issues of each curricular component – from learning objectives to criteria and techniques of assessment.

Taking into account the new professor’s functions, the features of today’s students, and the ever-increasing amount of knowledge, attention to the teaching method is a major issue. Currently, the teaching-learning process is enhanced by the adoption of active learning methods involving virtual environments [9] and problem-based approaches [10-12], which allow a more participatory teaching and meaningful learning [13,14].

In order to counteract the content-centered and decontextualized teaching

approaches for Biochemistry, it has been proposed a selection of key concepts [15,16]. In this way, the American Society for Biochemistry and Molecular Biology (ASBMB), supported by the National Science Foundation (NSF) has been suggesting the adoption of broad conceptual principles that guide teaching-learning in Biochemistry and Molecular Biology fields for life sciences' students. Aligned to this trend, an initiative led by the Association for the Advancement of Science (AAAS) named Vision and Change encourages modifications and adjustments in undergraduate biology education [17]. All these actions are related to five fundamental concepts: 1) evolution; 2) energy and matter transformations; 3) homeostasis; 4) biological information; 5) structure and function of macromolecules. The main purpose in highlighting broad themes is to ease their identification by students and to offer flexible topics for setting learning objectives and assessment methods.

In this paper, the strategy of using comprehensive and unconventional topics aimed at facilitating the link between molecular (invisible) issues and the visible context (body, environment...), using cooperative strategies (group work). Thus, we look for arousing curiosity, motivate study, and promote a deeper and long-term learning, by means of problem-situations that allow penetrating student's perception filters [18]. Furthermore, we seek students to learn a metabolic biochemistry in a more dynamic way, connected to all other disciplines of the Biology course, based on adoption of broad and interdisciplinary themes, in accordance with international curriculum standards (ASBMB/NSF/AAAS). Therefore, the hope is that metabolism study positively impact the biologist learning and training, contributing to make a unique professional.

Within this context, this work aimed mainly at describing the development and the application of two interventions organized as instructional materials – study guides – for students enrolled in a Biology course. These interventions were evaluated by using a qualitative approach, in order to assess their impact on learning through curiosity arousal and motivation for the study of metabolism – main subject of the target discipline.

2 Methods

2.1 Context and participants

The target discipline of this study, “Metabolism”, has 60 h and is offered in the second year, first semester, to two courses of Biology (daytime and evening) in a Brazilian

public university. There was a total of 85 students enrolled, divided in two groups: cohort A (daytime class, 42 students) and cohort B (evening class, 43 students). In both courses, the content of the Metabolism discipline complements that studied in the previous discipline, “Biochemistry of Proteins”, which emphasizes protein structure and enzyme kinetics. As for Metabolism, the core deals with components, regulation, and integration of the main metabolic pathways – carbohydrates, lipids, and amino acids.

The authors have direct (one of us as professor) and indirect (the other as researcher) involvement with the target discipline; aside from us, there is a professor in charge and four teaching assistants. According to the professor, in order to make the subject more interesting and extend the focus to different organisms, the discipline has been connecting unusual topics to the content, e.g. comparative biochemistry, searching for examples in the diversity of living beings. In this way, new uncommon themes were sparsely inserted in Metabolism, as evolution, metabolic adaptation, and phylogeny, linking them to the metabolic routes.

For instance, the study of the Krebs cycle components, functions, and regulation was supplemented with evolutionary data, seeking amplifying the context of the cycle – thus, rendering a novel meaning to the study of metabolism. The insertion of the themes was carried out by application of three study guides, especially developed for drawing students’ attention and foster their active involvement.

At the same time, visual tools for biochemistry teaching were implemented in Metabolism, like a software that simulates a classroom and an augmented reality application. Thus, the discipline looks for using a variety of teaching methods, including traditional ones – the sequence of themes and proposed activities are shown in Table 1. It should be emphasized that the study guides applied in days 4, 6, 13, 18, and 21 provide concise information interspersed with guiding questions for content study. Therefore, they differ from those materials which are the objects of this research – from now on represented by “SGs” (“Study Guides”).

For ease of identification of each SG, they will be referred to as “SG followed by a number (corresponding to the chronological order of application) plus a keyword”; so, “SG1 (Krebs)” corresponds to “Krebs cycle and Evolution”, “SG2 (Glycogen)” to “Metabolism of Glycogen – Comparative Biochemistry and Metabolic Adaptation”; and “SG3 (Glutamate)” to “Metabolism of Glutamate”.

Table 1. Programme of the Metabolism discipline in 2015, from March to June, showing the sequence of themes and activities of cohort A, highlighting the application dates of the three SGs (lines in *italics*, days 9, 16, and 25).

Day	Date and theme	Method
1	March 04 - Discipline overview. Introduction to metabolism - muscle contraction	Use of iPads with instructional software
2	March 06 - Introduction to metabolism	Lecture
3	March 11 - Principles of metabolism regulation	Lecture
4	March 13 - Carbohydrate breakdown - Glycolysis	Study guide and use of iPads (augmented reality application)
5	March 18 - Carbohydrate breakdown - Glycolysis	Lecture
6	March 20 - Krebs cycle	Study guide and use of iPads (augmented reality application)
7	March 25 - Krebs cycle	Lecture
8	March 27 - Respiratory chain	Use of iPads with instructional software
9	<i>April 01 - Krebs cycle and evolution (SG1)</i>	SG
10	April 08 - Respiratory chain and free radicals	Lecture
11	April 10 - Anaerobic metabolism	Lecture
12	April 17 - Test I	Written exam
13	April 22 - Lipids breakdown - Ketone bodies	Study guide
14	April 24 - Lipids breakdown - Ketone bodies	Lecture
15	April 29 - Metabolism of glycogen	Lecture
16	<i>May 06 – Metabolism of glycogen – Comparative biochemistry and metabolic adaptation (SG2)</i>	SG
17	May 08 - "Lorenzo's oil"	Movie session
18	May 13 - Amino acids oxidation - Urea cycle	Study guide
19	May 15 - Amino acids oxidation - Urea cycle	Lecture
20	May 20 - Gluconeogenesis	Lecture
21	May 22 - Fatty acids biosynthesis and pentose-phosphate pathway	Study guide
22	May 27 - Fatty acids biosynthesis and pentose-phosphate pathway	Lecture
23	May 29 - Metabolism of nitrogen compounds	Lecture
24	June 03 - Regulation of metabolism	Lecture
25	<i>June 10 - Metabolism of glutamate (SG3)</i>	SG
26	June 12 - Metabolism integration	Assignment with music
27	June 19 - Metabolism integration	Lecture
28	June 26 - Test II	Final written exam

2.2 Methodological approach

This work was carried out as a Design-Based Research (DBR). Such research approach is suitable for the study of complex situations, as the one focused in this paper, which involves simultaneous interaction of variables related to the learners and their activities, to the environment, and to the professor. In this way, DBR presents central characteristics [21,22] like: i) it is interventionist, involving some degree of planned intervention; ii) occurs in a naturalistic context, that is, the classroom; and iii) combines quantitative and qualitative techniques of data collection (mixed methods). DBR emerged in early 1990s [19] as an alternative educational research, opposing to the traditional psychological approach (experimental conditions, isolation of variables, and hypotheses

tests). It has been awaken interest in various fields, including Biology [20].

In practice, DBR involves iterative cycles that comprise: analysis of a real problem in its context, design of one or more interventions based on theory and practice, application of the intervention and evaluation of the whole process, particularly the theoretical and practical impact of the intervention. After frequent information exchange between researchers and professors, the cycle is resumed, with context reanalysis, improvements and application of new interventions, and so on. At every cycle, keeping in mind the intended goals, the researcher aimed at improving theory and practice in light of the performed design (intervention).

In our study, the theoretical-practical approach by using problems and broad themes in biochemistry learning supported and guided the planning of the interventions (namely, the SGs).

In this work, DBR was developed on the basis of mixed methods research [23] with embedded design [24], which involves simultaneous and/or sequential collection of quantitative and qualitative data. So, we assume that one of the data corpus (in the case, the qualitative) supports the other (quantitative), adding to illuminate the situation under study. All research procedures related to the interventions (please see next section – Data Collection) were approved by the local University Ethics Committee, receiving the number “39694714.1.0000.5404”.

2.3 Data collection

Data collection was carried out by qualitative and quantitative techniques [24]. Classroom observation and interview were applied as qualitative techniques; quantitative data were obtained in written tests and final grades reports.

2.3.1 Classroom observation

Inside classroom, the researcher neither involved in activities nor answered to questions or doubts – this role was left to professors and teaching assistants. So, it was clear for students the researcher’s role as non-participant observer. The focus of the observations was on students’ behavior during SGs (commitment to the activities, posed questions, involvement in discussions).

The total time of observation comprised 30 hours, registered by note-taking using clipboard and pen. The researcher carefully moved between students’ groups, striving for not disturbing ongoing discussions and instructors’ actions.

2.3.2 Interviews with students

Interviews were semi-structured and individualized, conducted by the researcher. The script contains nine questions (see Appendix C), each one with its own objective, as presented in Table 2. The main goal of the questions was illuminate the central aspects involved in SGs' application.

Table 2. Main themes and objectives related to the questions asked in students' interviews.

Question core	Objective
1. Positive and negative aspects of the SGs	Specifically assess the three interventions
2. SGs' impact on learning	Assess the degree of contribution of the SGs to metabolism learning
3. Interaction with classmates during questions' discussion	Assess cooperative work
4. Use of augmented reality application	Assess the impact of experiencing a visual resource
5. Instructors' feedback	Assess professors' and teaching assistants' support in classroom
6. Propensity for great areas of Biology	Assess if SGs' themes were interesting, based on preference for a specific area (molecular or environmental)
7. Impact of the discipline in biologist' training	Assess the contribution of the discipline to the professional training
8. General suggestions	Check emergence of new ideas or themes for raising interest in the discipline
9. Additional comments	Provide opportunity to further information or any corrections

The main selection criteria were genre and performance on a question in test I, in addition to professors' referral. In this case, such intentional selection can allow a greater understanding of the focused phenomenon [24]. Four students of each cohort (A and B) were invited to the interview, with guarantee of anonymity. During interviews, the researcher took brief notes and, at the end, reconstructed testimonies and send them by email to each interviewee. The students' selection process and interviews' procedures are described in detail elsewhere [25]. Only one interviewee did not return email confirming testimony – the student “5” (cohort B); therefore, it will be presented results from students “1”, “3”, “6”, “7” (cohort A) and “2”, “4”, “8” (cohort B).

It must be emphasized the significant time span between SGs' application and carry out of the interviews. For instance, the last planned intervention, SG3 (Glutamate), was applied on June 10, 2015. We opted for not bother students in the end of a heavy semester (seven final exams to fulfill). Thus, the interviews were scheduled after July holidays, for August 18 and 20, 2015; that is, five months after SG1 (Krebs) application, four months after SG2 (Glycogen), and two months after SG3 (Glutamate). These time lapses increase even further the testimonies' impact, revealing a high degree of grasping of the activities.

It also should be noticed that part of the answers to questions 3 and 5 was already

published [25], comprising positive comments about peer interaction (question 3) and praises to instructors' feedback (question 5). Answers to question 6 were vague and did not yield significant information. Then, in results' presentation, the focus will be on answers to questions 1, 2, 7, and 8 (see Table 2), which evaluate the impact of the SGs from several angles.

2.3.3 Quantitative data

The students' performance in one of the questions pertaining to the test II and the final average grades represented the quantitative data. The latter provides a general idea of the impact of all discipline's activities – including the three SGs – by offering an overall picture of the global performance of both cohorts throughout the semester.

2.3.4 Data analysis, interpretation, and validation

Qualitative analysis was carried out in stages. First, field notes (classroom observations) and interviews' testimonies were transcribed. Second, it was realized a cursory reading of the transcripts, in order to obtain a general idea. Then, an immersive reading was performed, aiming at selection of significant excerpts and attribution of codes. Finally, selected codes (secondary ideas) were grouped by similarity to form categories or general themes (main ideas). Considering the embedded research design, the quantitative analysis was carried out after the qualitative one, and their results were compared.

The results and their interpretation were validated by triangulating different data sources, looking for confirming evidence from different people, data type, and moments. Furthermore, confirmation by participants was performed in two ways: i) with interviewees, to whom was sent the whole testimonies' register for content checking; ii) with professors, based on annual research reports to verify completeness and validity of the results.

3 Description of the interventions

The interventions corresponded to the SGs' application and took place in three moments. Taking into account the content sequence of the Metabolism discipline, each SG was allocated in a specific point, so that they keep an equidistant position in time along the semester (see Table 1).

The full research span covered three years, from 2014 to 2016. The 2014 year was important as a pilot study, in which was applied for the first time two SGs (Krebs and

Glycogen) and came up the idea of the third (Glutamate). Once the discipline has been offered in the first semester, the research field encompassed three non-consecutive semesters. Thus, in semesters without the discipline, there was time enough for analysis and refinement of the material. The main data corpus was collected in 2015 since the three SGs were applied, analyzed, and evaluated. In 2016, due to policy issues which culminate in interruption of the academic activities in mid-May, it will only be presented brief classroom observation notes on SG1 (Krebs) and SG2 (Glycogen).

This paper emphasizes two SGs – the SG2 (Glycogen) and the SG3 (Glutamate), once the processes of development, application, and evaluation of the SG1 (Krebs) was recently published [25]. However, we present and discuss results related to this SG (mostly unpublished), since they provide support to illuminate the complex situation under study and offer a complete overview on assessment of the three materials.

In the next section it will be detailed the process of development and placement of SGs 2 and 3, followed by the results of their application. The full and updated content of the two SGs is found in Appendixes A and B. There are no additional materials available online.

4 Development of SG2 (Glycogen) and SG3 (Glutamate)

4.1 SG2: Metabolism of glycogen – comparative biochemistry and metabolic adaptation

Themes like *comparative biochemistry* and *metabolic adaptation* attract Biology undergraduates' attention because facilitate comparison among organisms from different kingdoms and exhibit the multiplicity of challenges faced by living beings, from microorganisms to plants and animals. Connect these perspectives to the study and learning of the metabolic pathways can contribute to motivate study and enhance learning. In Metabolism discipline, after SG1 (Krebs) application, the students attended classes on respiratory chain, oxidative phosphorylation, breakdown of lipids and amino acids (see Table 1). Thus, with emphasis on catabolic pathways, the study of comparative biochemistry and adaptation was linked to glycogenolysis.

The main reason for the choice of glycogen lies on previous years, when glycolysis and Krebs cycle had already been discussed from a comparative biochemistry viewpoint. Consequently, it was convenient to place SG2 far from the days those pathways were approached.

In this context, in 2014, SG2 (Glycogen) was developed and applied. As well as SG1 (Krebs), it was organized in three inter-related parts: the first part (Part 1) brings a problem aimed to contextualize the theme and motivate reading of the next part, which contains an informative text followed by bibliographic suggestions and/or references (Part 2); eventually, the Part 3 presents questions for discussion.

The first step of development consisted on a bibliographic review. Due to scarcity of those themes in educational publications, it was a hard task to retrieve information, whether in books or journals. The problem (Part 1) was elaborated in such a way to highlight that all living beings are prone to environmental constraints, to which they must face (i.e. adapt) somehow. There is also a link with evolution and the problem ends pointing out that adaptation may be advantageous, stimulating curiosity for reading the text.

The text (Part 2) is divided into two sections – Comparative Biochemistry (Section 1) and Metabolic Adaptation (Section 2). The Section 1 is composed of data on history and scope of comparative biochemistry, along with comparative details about glycogen stores, pathways, and regulation [26]. The Section 2 presents at the beginning the types of challenges imposed by environment and the living beings' general strategies for overcoming them. Soon after it brings curious data on extremophiles and describes a range of adaptations in different organisms, highlighting the problem to be faced and the strategy of each organism to deal with, focusing on glycogenolysis role as part of the problem solving [27].

The questions in Part 3 aimed at prompting students to link glycogenolysis with diverse mechanisms of adaptation, fostering interpretation of the data presented in the text. They were also a stimulus for a comparative view on glycogen metabolism. For instance, one of the proposed questions involved access and browsing in the KEGG¹ site, a huge database about biological structure and function in several levels (from molecules to organisms). Once accessed the site, the task was locating glycogen synthesis and breakdown pathways and select some organisms, in order to compare their metabolic maps in relation to the enzymes' use (the site allows to view, highlighted in color, whether the enzymes are expressed or not by a certain organism).

The preliminary version of the SG was discussed on May 14 (2014) with professors and teaching assistants of the Metabolism discipline. As a result, suggestions were included throughout the text (basically terminological issues); the questions were approved without modification.

1 Kyoto Encyclopedia of Genes and Genomes – www.genome.jp/kegg.

4.2 SG3: Metabolism of glutamate

In the last weeks of the discipline, one of the biggest challenges is providing ways of integration for the studied metabolic pathways, seeking motivating study and a deeper learning. With these purposes in mind, we developed and applied a SG based on a compound that allowed the integration of the contents seen in each pathway.

Such compound must be a molecule present in the final third of the discipline content, for example, a nitrogen compound. In addition, it should meet three other requirements: i) have been well-researched, with a large number of publications; ii) have a presence in diverse kingdoms (bacteria, protists, animals, plants, fungi); iii) to be comparable among different organisms, based on the ways of acquisition (origin and/or uptake) and functions. In principle, the last two conditions would allow to obtain information about adaptation strategies and comparative biochemistry.

The first (and key) question to be answered was: *which* molecule? For this purpose, we started from a Google search with the sentence “ubiquitous metabolite in biology kingdoms”. One of the results was more attractive: a comment titled “The small world of metabolism” [28] pointed to the amino acid *glutamate* as a central molecule in bacterial metabolism. This initial clue directed new searches in scientific databases (Pubmed, Web of Science), which reinforced the essential role of glutamate in several kinds of living beings.

Therefore, we justify the choice of glutamate because it is ubiquitous, multifunctional, and studied in the discipline in its final third, i.e. in the intended content’ zone for that intervention. Thanks to these characteristics, glutamate could be approached from a comparative biochemistry standpoint, in terms of its diverse forms of acquisition and use by different living beings, from microorganisms to plants and mammals. Thus, the conventional view of glutamate as a protein component was expanded and linked to adaptive and/or regulatory mechanisms in several groups of living beings, permitting the interconnection of this molecule with neurophysiology, plant physiology, zoology, microbiology, and so on.

Once set the molecule, it was carried out a broad bibliographic review for information collection, bearing in mind the aforementioned requirements. The results showed two categories of publication: one having a more global focus [29] and another bringing specific information about glutamate in various kingdoms. Thus, SG3 (Glutamate) was divided in two sections: a general part (Introduction) and special divisions – glutamate metabolism in mammals, plants, bacteria, and yeast. In the end, it presents questions to

debate; one of them asks for accessing a new website, named ExPasy², a Swiss biotechnological portal which presents a different view of the KEGG's metabolic pathways.

Although this SG diverge from the two others by not stating an initial problem, its introductory part aims at attracting students' attention to the integrative nature of the content, and seeks stimulating reading of further information. As a whole, data presented in the SG allow an integrated approach of all studied contents since embed a discussion on glutamate metabolism in relation to different metabolic conditions (fasting, fed state) and to functional diversity (including in the cell signaling), aside from highlighting its relationship with other studied metabolic pathways and adaptive mechanisms in diverse organisms.

5 Results

5.1 Application of the study guides (SGs)

5.1.1 *The year of 2014: a pilot study to the two first SGs*

As described, two problem-based instructional materials were developed and applied in 2014, SG1 (Krebs) and SG2 (Glycogen). The researcher was present in classrooms with cohorts A and B for SGs' application (SG1 and SG2), in order to make informal observations about the early impact of these materials. The dates of application were especially allocated in content sequence, according to the features of each theme. For instance, SG1 (Krebs) was applied in the sixth class, right after two lectures on metabolism introduction and its principles of regulation, and two classes on carbohydrate breakdown (glycolysis).

In 2014 and 2015, the SGs' application followed the same procedure, described in the next paragraph. The full activity lasted around 2 h; the first hour was reserved for individual reading of the material, and the second for a collaborative discussion in small groups, supported by professors and teaching assistants.

First, it was handed out a printed copy of the SG to each student. After a brief introduction on SG's organization, the professor explained that Parts 1 and 2 (respectively problem and text) should be individual and carefully read, whereas Part 3 (questions) should be discussed in small groups. Along the reading, if they found any unknown words or expressions, all they need was to ask instructors, who promptly clarified the doubt. Furthermore, he informed that students could freely consult textbooks. On average, six

2 SIB Bioinformatics Resource Portal – www.expasy.org.

groups were formed, with around six students in each. The role of the professors and teaching assistants consisted mainly in helping students in Part 3, by means of posing new questions for guiding discussion.

In general, based on student feedback to professors and teaching assistants, the SG arouse curiosity and fostered peer discussion. At the end of the discipline, the professor suggested to develop a third study material (Metabolism of glutamate), aiming at integration of the studied topics. Thus, three study guides were applied in 2015.

5.1.2 The year of 2015: second application cycle of SG1 (Krebs) and SG2 (Glycogen), and application of SG3 (Glutamate)

In 2015, SG1 and SG2 were applied in a second round, besides SG3 first time application. Next, details of each intervention are described.

SG1 (Krebs) – second cycle. SG1 was reapplied in the ninth class, right after three lectures regarding an introduction to metabolism and its principles of regulation, four classes on carbohydrate breakdown (glycolysis) and Krebs cycle, and a tutorial on respiratory chain.

In classroom observations, the researcher noticed the emergence of doubts during discussion, as well as unexpected issues like the possible reasons for dinosaurs' extinction. Also, there was a trend to precisely locate the "right" answer in the text. It should be pointed out that Part 3 is not to be worked as a questionnaire, but rather as a guide for exchanging ideas, exploring possibilities and expanding learning. Thus, there is no sense in trying to pick out definitive or correct answers.

Overall, the researcher witnessed the students' commitment to read and discuss, suggesting that SG raised curiosity and stimulated peer discussion, as lately confirmed in interviews (see details in Discussion).

SG2 (Glycogen) – second cycle. In the reapplication of SG2, in sixteenth class, students received Ipads: first, to allow access to KEGG's site, as part of one of the questions; second, to ease access to biochemical content for those who did not bring textbooks. In this case, before start to read the text, students should select unknown words and, as a group, search Internet for identifying and discussing them.

Application of SG3 (Glutamate). The procedures for application of this SG in twenty-fifth class was similar to the other two SGs, with individual reading and group discussion. Tablets were provided to students for access to Expasy portal, as part of one of the questions. It was noticed some difficulty in browsing, in part because of the idiom

(English). However, the activity took place smoothly, with students calling professors for asking questions, mainly doubts related to amino acid metabolism in human tissues.

5.1.3 Overview of students' engagement in SGs

Along the application of each SG, the researcher observed full involvement of students in the proposed activities, as evidenced by silence and focus in reading, and by participation in group discussions. It is noteworthy that, during the period of text reading, the majority of the students used highlighting color pens or, less frequently, pencils and ballpoint pens, to underline text passages.

Most of the time during peer collaboration there was one or more instructors engaged in meeting students' requests. Confirming researcher's observation, the professor mentioned that some groups were more committed than others.

5.1.4 Quantitative results

5.1.4.1 Question in test II

In order to link the theme of SG2 (Glycogen) to understanding of a key metabolic concept, the energetic balance, it was created a question with a contextualized situation of glycogen utilization. This question was included in test II. As there were two cohorts, A and B, two questions were created, based on different situation-problems but bearing the same final question text (see Appendix E).

It should be noticed that there was also a difference in test structure for the two cohorts. In cohort A test, the student should choose, among 10 questions, only eight to answer. Thus, 15 out of 42 students who took the test did not select the question. From those who did, around 44% made the correct option (glycogenolysis) along with the correct explanation (saving of one ATP because glucose was already phosphorylated when leaving the polysaccharide). However, nearly 19% incorrectly stated that glycogenolysis expends more ATP than glycolysis. Yet in cohort B test, all questions must be answered. Approximately 23% of the 43 students got a full grade in the question (correct option and explanation); another 30% incorrectly explained that glycogenolysis is more expensive than glycolysis, and around 9% did not answer at all (left out the question).

Although the percentage of success in the question seems poor, especially in cohort B, it should be highlighted that test II is far more demanding than test I, in terms of

complexity and content amount. As showed in the themes' sequence at Table 1, test I asked for sequentially related catabolic pathways, only involved in carbohydrate metabolism (glycolysis, Krebs cycle, respiratory chain...). Yet, test II encompassed both anabolic and catabolic routes from two complex macromolecular groups (lipids and proteins), in addition to pathways related to glycogen and to nitrogen compounds.

5.1.4.2 Final average grades of the students

The figures of students' final average grades in both cohorts (see Figure 1) indicate a good global performance in all proposed activities of the Metabolism discipline. The final average grade is composed by: Test I grade x 0.4 + Test II grade x 0.4 + average grades in assignments and small tests x 0.2. Taking into account that the minimum average grade to pass is five (5.0), the final average grades were high – the figures were equal or higher than 7.0 in 57% of the students (cohort A) and in 37% in cohort B. There was only one failure in cohort A and two in cohort B.

Figure 1. Graphic distribution of the final average grades in Metabolism discipline (in 2015).

6 Discussion

In-depth reading of the records from classroom observation (2014 and 2015) and interviews (2015) revealed a number of codes or key terms. They were grouped in four main categories for analysis: “interest”, “motivation”, “learning”, and “difficulties”. Next, each of these categories will be discussed, highlighting the assigned codes and its source (observation or interview) – for the sake of concision, consider the following abbreviations: Obs = classroom observation; Std = student (in this case, the source is an interview).

Here we also point out the clues leading to text alterations in SGs, mainly in SG2 (Glycogen), which underwent a change in structure (inclusion of a new section) and updates in some pieces of information.

6.1 Indicators of interest and redesign (alterations) in the SGs

Though interest and motivation may be somehow interconnected, e.g. by curiosity, we believe that interest for a subject is prior to the desire to study it thoroughly.

The appearance of unexpected ideas, coded as “outliers”, was regarded as an indicator of aroused interest for SGs. This was the case for dinosaur’s mass extinction, discussed by one of the groups (Obs., cohort A, SG1, 04/01/2015). An interesting question occurred during SG3 (Glutamate) discussion: a student asked the professor if, considering the acquisition of *non*-essential amino acids, the source of protein (animal or plant) matters (Obs., cohort B, SG3, 06/09/2015). The researcher observed, at the end of a class, a student from a group that had just finished question discussion. This group had already impressed the researcher by its engagement in reading and discussion, and that student keep asking some questions about the table [25] located in SG’s text (Obs., cohort A, SG1, 04/01/2015).

In the case of table 1 from SG2 (Glycogen), a student called the professor and said to have understand that “barophile” concerns to high pressure and “piezophile” to low pressure; the professor corrected, emphasizing that both refer to high pressures (Obs., cohort B, SG2, 05/05/2015). Another time, still regarding table 1 (SG2), the professor mentioned to find weird the presence of information about human beings in a table related to microorganisms (he referred to temperature and oxygen pressure data – see Appendix A). These indications, together with a suggestion from both a student and the professor to include something about phylogeny, were enough for proceeding to significant alterations in SG2 (Glycogen), which are described afterwards (see Appendix A for updated SG2).

Before the alterations, SG2' text presented first the comparative biochemistry, followed by the section of metabolic adaptation. Such structure was applied in 2014 and 2015. For 2016, the alterations were: i) the SG's title was modified, reflecting the change in content sequence – metabolic adaptation was moved to the beginning of the text (right after the problem), followed by a phylogeny section and eventually comparative biochemistry; ii) the Table 1 was updated by withdrew of human references and by data review on radiation, pressure, desiccation, and oxygen tension; iii) information on phylogeny and homology [30] were included and geared as much as possible to glycogen metabolism.

A specific point in Part 1 of the SG2 (Glycogen) must be highlighted. The problem ends with the following statement: "The high energetic cost needed to maintain these features is fully compensated by great advantages". Such phrase was aimed at motivating students to read the text, but also could lead to discuss which would be those great benefits. For instance, the high energetic cost is covered by the great amount of food intake that supports mammals' metabolic rate. Such rate is, approximately, from four to seven times higher than those needed to maintain a reptile with a size equivalent to a human being. However, being able to keep a constant internal milieu and a higher body temperature grants significant advantages to mammals and birds, like the ability to remain active even in adverse environmental situations and the necessary conditions to carry out more complex brain functions.

A frequent code was termed "doubts". For instance, a group wished to know if the redox processes only occur with coenzymes (Obs., cohort B, SG1, 03/31/2015). This is quite a usual doubt and refers to oxidation and reduction concepts. Clarify it is important since coenzymes' role as electron carriers implies that not only they have its redox state (oxidized or reduced) modified, but also other metabolites are able to act as electron donors or receptors, thus oxidizing or reducing themselves. Another interesting doubt was about the figure portraying the two primitive arms [25], in which a student asked whether or not bacteria were capable of carrying out only *one* of the arms (Obs., cohort B, SG1, 03/31/2015).

One of the difficulties in the development of instructional materials is the creation of questions which yield *discussion* that is, open-ended enough to allow to exchange of ideas and/or generation of hypotheses, thus involving higher cognitive operations [31]. In relation to the SGs, it is a great challenge to elaborate more intellectually demanding questions that also avoid easily found answers in the text. Certain questions may only arouse in

students the desire to confirm the expected answer, rather than a will to expand reasoning.

Sometimes, the discussion may be hampered by ill-structured questions. This was the case for one of the questions in SG2 (Glycogen) in 2014 – in next year of SG2 application, it was replaced by another question on tissue distribution of glucose transporters, which fitted in SG's context and fostered discussion (see Appendix D for the two questions). However, the new question led to unexpected outcomes. It proposed to discuss possible consequences of a hypothetical inversion of glucose transporters between two vital tissues, yielding a range of doubts and disagreements in cohort A (Obs., SG2, 05/06/2015) and in cohort B (Obs., SG2, 05/05/2015). It must be pointed out that both cohorts attended, in the first days, two lectures concerning introductory notions on hormonal roles (including insulin) and types and functions of glucose transporters. So, we opted for withdraw the question of the SG2 applied in 2016.

The professor, in an informal comment to the researcher, noticed a trend in some students to first check SG's questions and then proceed to text reading, trying to find prompt answers in the text (Obs., cohort B, SG1, 03/31/2015). In addition, students suggested making available the SG material before the class, and only attend class to question discussion (Obs., cohort B, SG2, 05/05/2015). Reading in advance can be a useful resource in some cases, e.g. in flipped classroom settings [32], but is not always recommended or easily implemented [33,34]. We believe that previous reading of a special material, unavailable in textbooks or papers, would be unsuitable for the proposed activity of focused classroom reading followed by discussion.

A student's doubt caused a small alteration in the introductory text in SG3 (Glutamate). She would like to know if aspartate and glutamine synthesis took place in all tissues; she had compared what was learned in class with the excerpt from SG3, which was unclear to her (Obs., cohort A, SG3, 06/10/2015). The professor explained and clarified her doubt. Indeed, the professor had warned the researcher against that passage. The excerpt, first paragraph of "Glutamate in mammals", should make clearer what happens in the liver and in other tissues as to the action of two key enzymes from amino acids metabolism – *aspartate aminotransferase* and *glutamate dehydrogenase* (the full and updated SG3 can be found in Appendix B).

Another ascribed code was "positive aspects of the SGs". This information came up in interviews and illustrate that SGs' impact had gone beyond the high degree of aroused interest: *the evolutionary aspects unified and helped understand the biochemical content; the questions were interesting and aided to guide thinking; the tables supported data*

comparison (Std 1, cohort A, 08/18/2015, who suggested including the theme phylogeny in a SG); I found the texts very good, I would like to have had more texts. [...] The glutamate's study guide helped me a lot in the exam because presented key sentences that supported understanding of the varied pathways from amino acids metabolism (Std 2, cohort B, 08/18/2015); ...the texts were curious, and provoked discussion. [...] I liked the study guide on glycogen, as it broadened the vision to other organisms, different from human beings (Std 4, cohort B, 08/18/2015); ...it was important to see how the pathway works in other organisms, with a more open and dynamic view. [...] It was a very productive experience (Std 6, cohort A, 08/20/2015); It was interesting because deviated from human being focus, comprising diverse organisms. The questions were important to come back to the text (Std 7, cohort A, 08/20/2015); It allowed to understand the amplitude and the complexity of the metabolism. The glycogen's study guide was interesting, once it permitted resume comparative physiology seen in high school... besides, it put aside human focus – all disciplines in this semester focuses human beings. In general, the three study guides were interesting (Std 8, cohort B, 08/20/2015).

6.2 Indicators of motivation and learning

As reported, students received tablets in the SGs with questions involving access to Internet. Nonetheless, it was noticed that some of them used their own mobile phones for web access. A student called the professor and, exhibiting to him the mobile screen, asked if it was a good site for viewing metabolic pathways (she showed the Expasy's site); the professor agreed, and confirmed such site would be explored in another SG (Obs., cohort B, SG1, 03/31/2015). This instance is revealing since the student by herself located and accessed an already predicted site to be browsed in SG3 (Glutamate).

One of the students was interested in the first reference of the Introduction in SG3; then, the professor clarified English terms and helped find the full article text (Obs., cohort B, SG3, 06/09/2015).

In an interview, a student expressed the wish to deepen information, to “learn to learn”, showing he appreciates critical thinking: *The most interesting is that it led to research more, adding to our scientific training. The references at the end of each text helped to complement information; they teach students to search for information by themselves. In addition, they aided in part the study for the test. [...] I would like to suggest that, at the end of each class, it would be recommended a journal article related to the theme because it could help show how science is dynamic, how every statement or image*

explored in class has something behind them – such reading would aid to understand how things are developed, and not only just accept content as something ready and finished (Std 6, cohort A, 08/20/2015).

6.3 Analysis of the SGs' whole impact on learning

The learning we would like to highlight here is different from rote or mechanical one. It is pointed out the long-lasting learning, acquired by means of a social constructivist approach [35], which values students' previous knowledge, building new perspectives to what is already known, thus grounded in meaningful learning [13]. In this regard, the SGs were developed not only for individual reading activity, but also to be discussed interactively, under guidance of the proposed questions. The SGs' contents communicate with each other, mutually strengthening on the basis of a background involving history (evolution, phylogeny), comparative studies (diversity of organisms and adaptations), applied perspectives (micro versus macro relationships), and interdisciplinarity [17]. Thus, they help to inter-relate the macroscopic and submicroscopic worlds, a required skill for achieving meaningful learning since it promotes understanding of abstract concepts of metabolism.

The classroom observations were helpful for grasping students' reactions before the applied materials. Nonetheless, the actual SGs' impact was revealed by questions and answers in the interviews. For instance, the question 2 directly approached the learning issue: "How do you evaluate the impact of these materials (study guides) on your learning of the metabolism?". The most illustrative answer was the following: *In a very positive way. Starting backwards, "Metabolism of glutamate" complemented the view on amino acids metabolism; that material concerning Krebs cycle from an evolutionary stance was a good example... The study guides boosted interest by evolutionary thinking – in light of evolution, things make sense since it broadens our vision on biological phenomena, prompting will to study* (Std 1, cohort A, 08/18/2015). This testimony provides strong evidence that the material not only pleased the student, but also motivated him to expand knowledge.

Furthermore, the student 1 provided new evidence that his learning transcended disciplinary boundaries, when asked if the discipline was important to professional training: *It was very important. I loved biochemistry. It helped understand other disciplines, like physiology (human in principle since we did not attend animal physiology yet), concerning functioning of live organisms, and histology. It was essential to unite concepts of cell*

biology and cellular signaling, important to exceed the mere descriptive and decontextualized knowledge. The evolutionary aspects supported understanding of family relationships, both from environmental and molecular phylogeny viewpoints. It was very positive to have watched the movie “Lorenzo’s Oil” and have attended the proposed activity – this experience made me realize that biochemistry is everywhere and, inspired by the movie, I wished to study the diseases and the pharmacological methods utilized to fight them (Std 1, cohort A, 08/18/2015).

At the end, he added: *Search for new ways of teaching is important – this is an advantage of Biology, the fact of being dynamic, visible; didactic resources are fundamental, like the study guides, the augmented reality application... The excess of memorization should be avoided, due to a great deal of names and very descriptive processes – it is necessary to like biology, and the study guides made for it (Std 1, cohort A, 08/18/2015).* Together with another student’s testimony – *...few disciplines take care of didactics, as is the case for Metabolism (Std 6, cohort A, 08/20/2015)* – reveals that students acknowledge the importance of didactic planning for learning of complex subjects, like metabolism.

The feature of knowledge integration, provided by the way SGs’ texts were built, there was already showed up in a former speech (Std 1, cohort A). Next there is another testimony which resume and reinforce this aspect: *Mainly in the third study guide, the access to the site was impacting as to showing metabolic pathways’ integration, how everything is connected; the Krebs cycle study guide had the same impact, in the sense of integrating knowledge (Std 8, cohort B, 08/20/2015).*

Considering the importance for the professional, other speeches were favorable, revealing that the desired bridge between micro- and macro-universe was successful: *I love it. Use of real daily examples, linking with real life. It is very interesting to know what is happening in our own organism, this is important to every professional, not only from Biology (Std 2, cohort B, 08/18/2015); It is one of the core disciplines, which allows to understand how survival of the organism takes place. The metabolism is essential both for research and teaching since it is capable of raising interest for science in classroom (Std 3, cohort A, 08/18/2015); It was essential – first, by encouraging research and guide searching for bibliographic sources; secondly, because it is interesting and makes me more curious, willing to know more and interconnect with other disciplines (Std 6, cohort A, 08/20/2015).*

By comparing SGs’ content with those found in textbooks, a student uncovered a

new SGs' effect on learning: *It was clearer to understand the processes; each textbook presents a different description of the pathways – the study guides' texts were very well explained. As a complex subject, it is required to keep an open mind, and in this regard the study guides' materials helped a lot to clarify the subjects* (Std 3, cohort A, 08/18/2015).

Taken as a whole, the testimonies reveal that the activities developed in the discipline value critical thinking and reinforce learning of scientific literacy [36].

6.4 Difficulties and indicators for additional alterations

The question involving access to KEGG's website presented two challenges for students – the idiom (English) and the browsing. For instance, a frequent doubt was related to the terms *branching* and *debranching*. As for browsing the site, a group found difficulty in localizing the protozoan *Toxoplasma gondii*, as the search engine by key words is limited (Obs., cohort A, SG2, 05/06/2015). Despite such difficulties, the professor commented that students were amazed at KEGG's variety of pathways in different organisms.

They also found similar difficulties in the other explored site, the Expasy (Obs., cohort A, SG3, 06/10/2015). A common doubt in both cohorts was *oxoglutarate*, which stands for *alpha-ketoglutarate*, a known compound by students. A student spoke in the interview: *...I found the metabolic map rather complicated* (Std 4, SG3, cohort B, 08/18/2015), the very usual opinion among biochemistry students. In order to minimize browsing hurdles, the professor suggested including reading of the legend information before navigating by the metabolic map. He also suggested, from question “3a”, the inclusion of a question with access to KEGG's site, with selection of some organisms mentioned in the text and searching for “glutamate synthase”, in order to check which of them actually express this enzyme. Thus, the question could be answered by evidence from a constantly updated database. The original rationale of the question was to show that Expasy's site exhibited an information – “plants do not express glutamate synthase” – which did not match those found in the text. Eventually, the suggestions were embedded in Part 3 of the SG3 and are available in Appendix B.

Some difficulties emerged in the interviews – they were coded as “negative aspects of the SGs”. For instance: *...many pages to read; it was hard to read due to noise at classroom – besides, since I like to read calmly, there was not time enough to finish reading. I suggest sending the text early* (Std 1, cohort A, 08/18/2015); *...the visual*

appearance of the study guides should be improved, for example, by including images, like in Krebs cycle' study guide (Std 3, cohort A, 08/18/2015); ...I thought the glutamate's study guide quite confusing because there was not a class for helping understand (Std 4, cohort B, 08/18/2015); Other questions were very easy; I found some aimless, like those related to KEGG's site, with very direct answers – in this case, it was cool to see how the site works, but there was not a question to make us think. ...I thought texts very long, there was not time enough for a calm reading (Std 7, cohort A, 08/18/2015).

It should be pointed out that SG2 (Glycogen) actually have no illustrations, but its updating included a figure on phylogeny (see Appendix A). In addition, the questions regarding access to KEGG's site were rewritten (so that became more meaningful) and moved to SG3 (Glutamate).

Another emerged code in interviews was “content hurdles”, which reveals not only specific difficulties, but also the challenge of integrating metabolic pathways: *I just did not understand the class about lipids, it is a very difficult pathway... I would like to attend that class again. I suggest an application to study the lipids (Std 2, cohort B, 08/18/2015); I did not like the way metabolism integration was conducted. I suggest that, at the end of the discipline, there was something for unite, integrate, organize the studied cycles; for example, a dynamic game would be interesting (Std 1, cohort A, 08/18/2015); I suggest a material about enzymes, different from what is found in textbooks, explaining their concept and functions. There was no time enough to study better this part (Std 3, cohort A, 08/18/2015).* As seen, besides spotting their difficulties, students also pointed out possible solutions to overcome them, indicating a willingness to cooperate for improving the discipline.

In other testimonies, the semester's duties showed up: *...the first semester was exhausting, we were always worried about demands of other disciplines... there was no time for studying and clarifying all doubts (Std 3, cohort A, 08/18/2015); There are many disciplines, you know? And not all of them care for didactic, as is the case for Metabolism (Std 6, cohort A, 08/20/2015).*

Two testimonies are revealing about the meaning of activities' set proposed by the Metabolism discipline, obviously including the SGs. One testimony was an answer to the question “Do you have any suggestions for raising your interest by the discipline?”. The student's response: *I am not sure... The classes were interesting, I wished to learn because, aside lectures, it also had room for think and do something (Std 7, cohort A, 08/20/2015).* In another speech, the student said: *The discipline was very productive,*

dynamic, with the applications, the study guides... (Std 8, cohort B, 08/20/2015).

As for quantitative information, they permitted illuminate the global context from two points of view. Firstly, regarding the test question, it was an attempt to link SG2' theme (metabolism of glycogen) to the understanding of a key metabolism concept, namely the *differential energetic balance*. Such concept deals with the energetic balance (expenditure versus production) in several conditions, e.g. presence or absence of oxygen, energy source, etc. Secondly, the final average grades confer an overview of the good performance in the whole discipline, providing a favorable scenario to metabolism learning.

6.5 Brief remarks about the third year of SGs' application (2016)

In 2016, by reason of force majeure, it was only feasible to apply and observe two SGs, the SG1 (Krebs) and the SG2 (Glycogen).

As reported, it was observed in some students a behavior of read questions before the text, resulting in an undesirable reasoning focus and earlier requests for help. Thus, in order to increase immersion and promote careful reading of the entire text, the dynamics of SGs' application was changed – first, the text was handed without the questions. Then, 45 minutes later, students received the questions for discussion. The researcher noticed that students were apparently more focused on reading.

During SG1 (Krebs)' discussion, a student asked an unprecedented question: *Where is Krebs cycle in this table?* (Obs., cohort B, 04/04/2016), speaking of table 1 in SG1 [25]. Though straightforward, the question embeds a profound questioning, which represents the core of the initially proposed problem: “in what moment there is a route effectively organized as a cyclic and aerobic pathway?”.

6.6 Suggestions for application in other settings

The SG1 (Krebs) can be applied *before* or *after* the respiratory chain. In the first case, it may foster reflection on reasons for Krebs cycle' ubiquity, yet without knowing its relationship with the respiratory chain by means of coenzyme reoxidation. On the other hand, if applied later, it can promote a deeper discussion on functions of the primitive “arms” [25].

The macro-theme “metabolic adaptation” is particularly helpful to be applied as a problem-based approach for Biochemistry teaching, or even in other molecular-based disciplines, due to the following characteristics: i) the problem is straightforward, depicted either by the difficulty being overcome or necessity to be supplied; ii) it can encompass

several life kingdoms, from bacteria to human beings; iii) the problem to be faced is often environmental, which favors a more comprehensive and integrative study; iv) it can be allocated in the beginning, middle, or end of the content sequence, allowing to be planned to show up in different metabolic pathways or to involve diverse macromolecules (carbohydrates, lipids, proteins, nucleic acids).

To come and go between nanometric scales and body dimensions, back and forth between picomolar concentrations and environmental scopes, is an important ability for biologists [37]. One of the research' goals was precisely carry out the bridge between micro- and macro-universe. The strategy of developing instructional materials which connect broad themes with contextualized problems- and/or questions-generating discussion can be exploited by professors in charge of molecular-based disciplines, as microbiology, immunology, cell biology, genetics, and, in many aspects, physiology. At first glance, linking an abstract theme to an applied, visible subject may sound an easy task, but it is not trivial when dealing with molecular issues [38]. Thus, building a problem aimed at interconnection of the micro- and macro-worlds demands higher level of thinking and attention. It is not only a matter of posing a problem to be solved, bearing a simple and single solution, but rather a motivating *situation-problem* which fosters divergent cognitive processes [39], allowing to generate new knowledge both individually and during peer interaction.

For professors going to develop instructional materials with SG-like structure we suggest first hand out Parts 1 and 2 (problem and text), and only later present questions for discussion (Part 3). In addition, in order to obtain more substantial information on discussion dynamics in small groups, it can be helpful to pay attention in classroom to the types of questions and speech sharing, as well as to include in interview script the following questions: i) "In each SG, express your opinion about whether the questions were well developed (yielded discussion, allowed to create hypotheses...) or were closed-ended (single answer, little debatable...)"; ii) "Do you think the speech in the group was well shared (for instance, everybody had the opportunity to express themselves?), someone ruled discussions, or there was other way of interaction would you like to comment upon?". The former question suggested can provide indications of the depth reached in discussion, and the latter may help identify difficulties and differences that naturally emerge in group interactions [40,41].

7 Conclusions

As a whole, qualitative and quantitative data allowed to evaluate the SGs' application in classroom, by supporting the findings related to the positive impact concerning interest, motivation to further study, and learning. For these purposes, one of the strategies was developing a problem that linked molecular (micro) and contextual (macro) levels. It should be highlighted that the choice of broad themes in order to carry out interconnection of micro- and macro-universe was not casual. In several points throughout SGs' contents, "micro-themes" (Krebs cycle, metabolic pathways of glycogen and glutamate) are linked to "macro-themes" (evolution, comparative biochemistry, metabolic adaptation), and vice-versa. For instance, although SG2 (Glycogen) focuses on metabolic adaptation and comparative biochemistry, it resumes evolutionary aspects by means of phylogeny; as for SG3 (Glutamate), comparative biochemistry is reinforced along with examples of metabolic adaptation.

On the other hand, there are limits to the SGs' application; whether used in an isolated way or in a traditional setting, based on transmission of information, they may be inefficient. Part of the positive results can be awarded to the discipline structure as a whole, which blends conventional activities (lectures) with active learning strategies, resulting in greater involvement of the students. For instance, aligned to the features of today's students, it uses resources like computer simulations, virtual games, and augmented reality, in addition to make use of unconventional assessments (e.g. a music-based assignment).

The use of problem-based approaches and active learning methodologies are nothing new in higher education [39]. In this context, the literature provides interesting examples, all reporting good results for learning: i) restructuring of contents by adoption of comprehensive themes and active learning settings [42,43]; ii) support by tutorials and open-ended questions [44]; iii) use of problems or questions especially built to facilitate the teaching of complex and interdisciplinary issues [45,46]. The novelty of the present research is the detailed record of development, application, refinement, and reapplication of teaching materials which implies both individual immersion and cooperative work group, based on hardly ever addressed themes in textbooks and/or scientific articles with didactic purposes.

To sum up, we believe that using broad themes, contextualized as problem-like situations and/or integrative perspectives, is helpful for learning metabolism in a deepen and meaningful way. We hope the SGs may have added to biologist training as

professionals since these materials expand the interdisciplinary character of the Biochemistry, connecting it with elements of evolution (history, timelines), microbiology (early life), physiology (adaptive processes), etc. Furthermore, there is also a hope that perhaps this work may inspire professors from biochemistry or other fields to develop and improve new teaching ways, aiming at a more active student engagement and a lifelong learning.

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