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Empirical evaluation of a virtual laboratory approach to teach lactate dehydrogenase enzyme kinetics

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HIGHLIGHTS

- We developed & implemented a specially-designed adaptive virtual-laboratory [vLab].
- Laboratory lactate dehydrogenase kinetics were taught to 2nd-year biochem students.
- The vLab was designed using HTML5 and hosted on an adaptive e-learning platform.
- The learning outcomes were on par with that from a conventional classroom tutorial.

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ABSTRACT

Background: Personalised instruction is increasingly recognised as crucial for efficacious learning today. Our seminal work delineates and elaborates on the principles, development and implementation of a specially-designed adaptive, virtual laboratory.

Aims: We strived to teach laboratory skills associated with lactate dehydrogenase (LDH) enzyme kinetics to 2nd-year biochemistry students using our adaptive learning platform. Pertinent specific aims were to:

(1) design/implement a web-based lesson to teach lactate dehydrogenase(LDH) enzyme kinetics to 2nd-year biochemistry students
(2) determine its efficacious in improving students' comprehension of enzyme kinetics
(3) assess their perception of its usefulness/manageability(vLab versus Conventional Tutorial)

Methods: Our tools were designed using HTML5 technology. We hosted the program on an adaptive e-learning platform (AeLP). Provisions were made to interactively impart informed laboratory skills associated with measuring LDH enzyme kinetics. A series of e-learning methods were created. Tutorials were generated for interactive teaching and assessment.

Results: The learning outcomes herein were on par with that from a conventional classroom tutorial. Student feedback showed that the majority of students found the vLab learning experience “valuable”; and the vLab format/interface “well-designed”. However, there were a few technical issues with the 1st roll-out of the platform.

Conclusions: Our pioneering effort resulted in productive learning with the vLab, with parity with that from a conventional tutorial. Our contingent discussion emphasises not only the cornerstone advantages,

Abbreviations: AeLP, Adaptive e-learning platform; CSS, Cascading Style Sheets; CTML, The Cognitive Theory of Multimedia Learning; HTML 5, Hyper Text Markup Language 5; JS, Java Script; LDH, lactate dehydrogenase; SaaS, Software as a Service; SD, Standard deviation; SDLC, Software development life cycle; UTAS, University of tasmania; vLab, Virtual lab; Vs., Versus; WYSIWYG, What-You-See-Is-What-You-Get.

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but also the shortcomings of the AeLP method utilised. We conclude with an astute analysis of possible extensions and applications of our methodology.

1. Introduction

Over the past couple of decades, biochemistry education has transitioned into a new paradigm, owing to several factors impacting higher education:

(1) Higher education has massified, resulting in a more diverse/large cohort of students with broader foundational skills [1].
(2) Internet and communication technology provide new ways of involving students in higher education [2] – intranational and international; urban and rural.
(3) Many students have cultural, family or part-time work commitments. An increasingly student-centric educational approach (like Learning Management Systems) has provided greater flexibility in course structure and delivery for them.
(4) Funding models have changed emphases by rationalising teaching resources to teach more students with less funding and requiring greater accountability for quality.

Computer-assisted learning, animated biomolecules [3], and simulated experiments [4–6] are no longer restricted to campus-computer use. They are widely disseminated via DVDs/CDs/USBs or the internet. Games [7] and computer-games have been used to actively engage learners in education. Numerous interactive laboratory courses in biochemistry are accessible free online [8]. However, barely a handful of these are genuine 3D-simulations of actual laboratory procedures or biochemical processes.

Virtual worlds and second life [9] offer new ways of garnering foundational skills for biochemical research that provide students with greater control over their study modus operandi. Adaptive e-learning [10] offers personalised education where a student may learn skills and assimilate concepts via a guided journey dynamically commensurate with their knowledge and skill-sets.

Online laboratory simulations can assist students from the outback to familiarise themselves with laboratory procedures before they attend sessions on their enrolled academic campus [4]. When simulations are integrated with other educational activities [11], they greatly accentuate learning. We chose an adaptive approach to deliver lesson-content owing to our awareness of our students' broad range of abilities. Enzyme kinetics is a topic which many students struggle with, an aspect which motivated us to develop an interactive simulation of an enzyme-based assay.

The students chosen for this study were 2nd year undergraduate students enrolled in an introductory biochemistry unit, having limited knowledge of chemistry/mathematics, and least-intending to undertake further study in biochemistry. Our objective of elucidating their comprehension of enzyme kinetics, translated into the following 3 specific aims:

(1) To design and effectuate a web-based lesson to teach basic enzyme kinetics to 2nd-year biochemistry students.
(2) To determine the efficaciousness of that lesson in improving grasp of enzyme kinetics; both content-, and skill-based. The teaching session was designed to:
   (i) conduct simultaneous enzyme catalysed colorimetric reactions using a microplate reader
   (ii) analyse kinetic data to determine the rate of an enzyme catalysed reaction and calculate the kinetic constants, K_m and V_{max}
   (iii) determine two-different types of enzyme inhibition by comparing calculated values of $K_{m(app)}$ and $V_{max(app)}$ in the presence of an inhibitor with the K_m and V_{max} of the uninhibited enzyme.
(3) To assess students' perception of the lesson's usefulness and ease of use

Our study summarises the design, implementation and evaluation of an interactive virtual lab for teaching lactate dehydrogenase (LDH) kinetics. We also describe a few hurdles which we encountered, as would commonly occur whilst utilising a pioneering web-based learning program.

2. Materials and methods

2.1. LDH kinetics experiment and data analyses

The LDH kinetics laboratory experiment designed by Powers *et al* [12], was modified by us for use with a 24-well microplate and the SpectraMax microplate reader. This microplate reader utilises Softmax Pro software version 5.3 (Molecular Devices, Germany). Each 1.2 mL assay run in glycine buffer (0.5 mol/L glycine with 2.5 mmol/L EDTA, pH 9.5) consisted of 0.7 U/mL LDH, 0.22 mol/L hydrazine and 1.2 mmol/L β-NAD^+. Across each of the 4 microplate rows, wells had varying concentrations of lactate (5, 25, 55, 75 and 95 mmol/L). An inhibitor (oxalate or oxamate) was added to each well in rows B (10 mmol/L), C (20 mmol/L), and D (30 mmol/L). The kinetic assay performed at 25 °C, was initiated with the addition of β-NAD^+. Absorbance (340 nm) was recorded at 20-s intervals for 5 min. Five replicate plates were analysed.

Velocity versus [substrate] Michaelis-Menten plots were constructed using Graph Pad Prism (version 6.02, San Diego California, USA) (Fig. 1). The plots pertaining to the reactions with oxalic acid are depicted in Fig. 1A, and the ones with oxamic acid are depicted in Fig. 1B. Each point represents the mean and SD for 5 replicate kinetic-experiments. The values for V_{max}, $V_{max\ app}$, $K_{m,}$ and $K_{m\ app}$ were calculated by fitting the data to a one-site binding hyperbola. The value of K_m and V_{max} (Supplementary file – Table) were 20.0 ± 5.6 mmol/L (95% CI 8.5–31.4 mmol/L, $r^2 = 0.864$) and 30.1 ± 2.2 μmol/L/min (95% CI 24.1–34.2 μmol/L/min, $r^2 = 0.864$) respectively.

2.2. Development of the virtual lab (vLab) using AeLP

We used the Adaptive eLearning Platform (AeLP) developed by Smart Sparrow™. This is a web-based set of tools for creating, publishing and analysing adaptive eLearning activities [10,13,14]. The AeLP runs as Software as a Service (SaaS), with a platform containing a What-You-See-Is-What-You-Get (WYSIWYG) author component. The Software development life cycle (SDLC) is the conventional depiction of the software development/management process targeting a specific objective. It consists of a series of phases. Our SDLC consisted of:

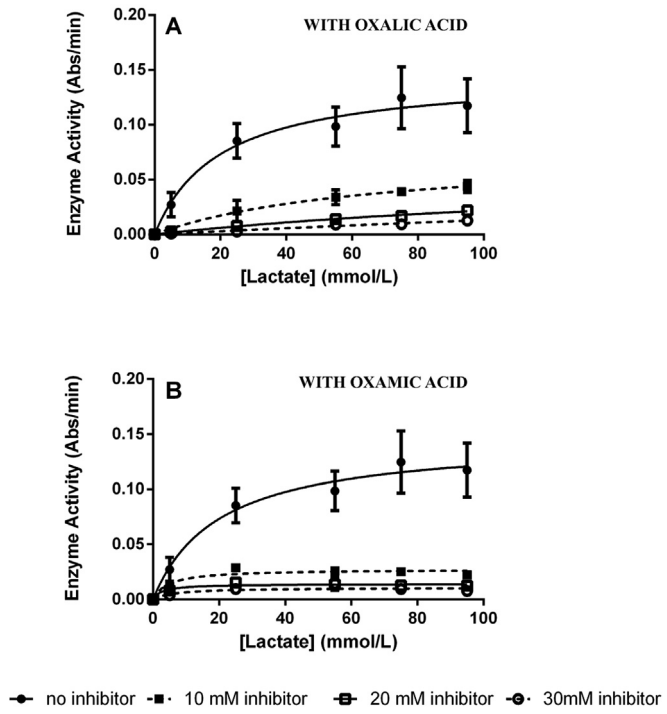

Fig. 1. Michaelis-Menten plots for the LDH assay in the presence and absence of inhibitors. (A) The reaction in the presence of oxalic acid. (B) The reaction in the presence of oxamic acid. Each point represents the mean and SD for 5 replicate kinetic experiments.

(1) Requirements and visual design: A lesson storyboard and LDH virtual lab (vLab) requirements were produced as a series of documents with descriptions for:

(i) physical laboratory processes
(ii) learning objectives
(iii) processes to be made 'virtual' versus demonstrated (video)
(iv) common student misconceptions and anticipated student errors
(v) student and vLAB interactions (use cases)
(vi) vLab lesson context (the exact nature of the vLab – lesson integration)
(vii) vLab scenes corresponding to distinct virtualised procedures
- Images and videos taken during the performance of a real LDH assay experiment were used to design visual assets
- vLab activities were scripted as discrete scenes (including a sequence of stages with feedback for anticipated student errors)

(viii) vLab components corresponding to real-life apparatus
(ix) vLab lesson interface to enable tracking of student interaction with the vLab in real-time

(2) Development: The LDH vLab was built using Hyper Text Markup Language 5 (HTML 5) technologies and consisted of HTML, Cascading Style Sheets (CSS) and Java Script (JS). The development environment included tools to support version control (code management), build process, and test applications to run a web browser. The resultant LDH vLab was consistent with storyboard and requirement documents produced at the *requirements and visual design* (1) phase.

(3) Quality assurance: LDH vLab components were test-analysed throughout the development process to ascertain usability and authenticity. Once all usability issues were addressed, the vLAb was accepted as ready to deploy.

(4) Deployment: This pioneering eLearning laboratory exercise was offered to introductory biochemistry students. The LDH vLab was accessed via desktop or laptop web browsers.

2.3. Particulars of the vLab student interface

The LDH vLab tutorial provided relevant information including content materials and instructions in a short series of slides, before the vLab experiment (pre-training principle) (Fig. 2A). This included an overview of the vLab experiment in video format (Fig. 2B). Prior to initiating the animation, students were provided with an overview of the steps involved in the vLab experiment (signalling principle) (Fig. 2C, D).

The actual animation included minimal text (such as volume of weight selectors); thereby avoiding excessive cognitive load. The visual elements within the animation were synchronised with text, by responding to the learner's interaction (temporal contiguity). Error messages appear in response to learner's mistakes (coherence principle). Spatial contiguity was maintained by placing text on or next to the objects in the virtual laboratory stage (Fig. 2C, D). Perpetual functions included 'restart lesson', 'history' and 'notepad' options in the top right-hand corner of the screen.

2.4. Evaluation of instructions posited by student interface

The LDH vLab users were posed sets of questions in order to check whether they understood the preliminary instructions. The LDH vLab permits students to anticipate their level of expertise by choosing from 3 problem-solving levels: normal, hard or challenging (Fig. 2A). Students who have more knowledge of terms associated with the exercise have the opportunity to skip some of the supportive information. However, if the student then feels they need to revise some of this information they also have the option to go back to the supportive information; or if they feel their level of expertise is greater than the level they originally chose, they can choose a more challenging level. In this way it is the learner who assesses their own expertise based on performance (score) and personal effort. Depending on the level, the learner traverses what he/she may encounter as worked examples, completion problems, conventional problems, or additional problem solving tips.

2.5. Study design

This study was approved by the University of Tasmania Human Research Ethics Committee. Written informed consent was obtained from all students participating in the trial. Consenting 2nd-year introductory metabolic biochemistry class students were randomly assigned at the beginning of the semester to either a vLab session (group A, n = 35) or a conventional classroom tutorial (group B, n = 34). The background content, including video material and sets of questions presented to each group were identical. In the conventional tutorial, the LDH experiment was presented using written materials and whiteboard, whereas the vLab students completed all their work online including a simulated LDH experiment. Students in the vLab group were also able to generate raw data, insert and produce their kinetics graphs (Fig. 3).

(1) After the completion of the vLab lesson, student pathway and understanding of the LDH vLab was assessed using the AeLP analytics; based on correct and incorrect answers, number of attempts to complete a question, and the difficulty-pathway-choice selected.

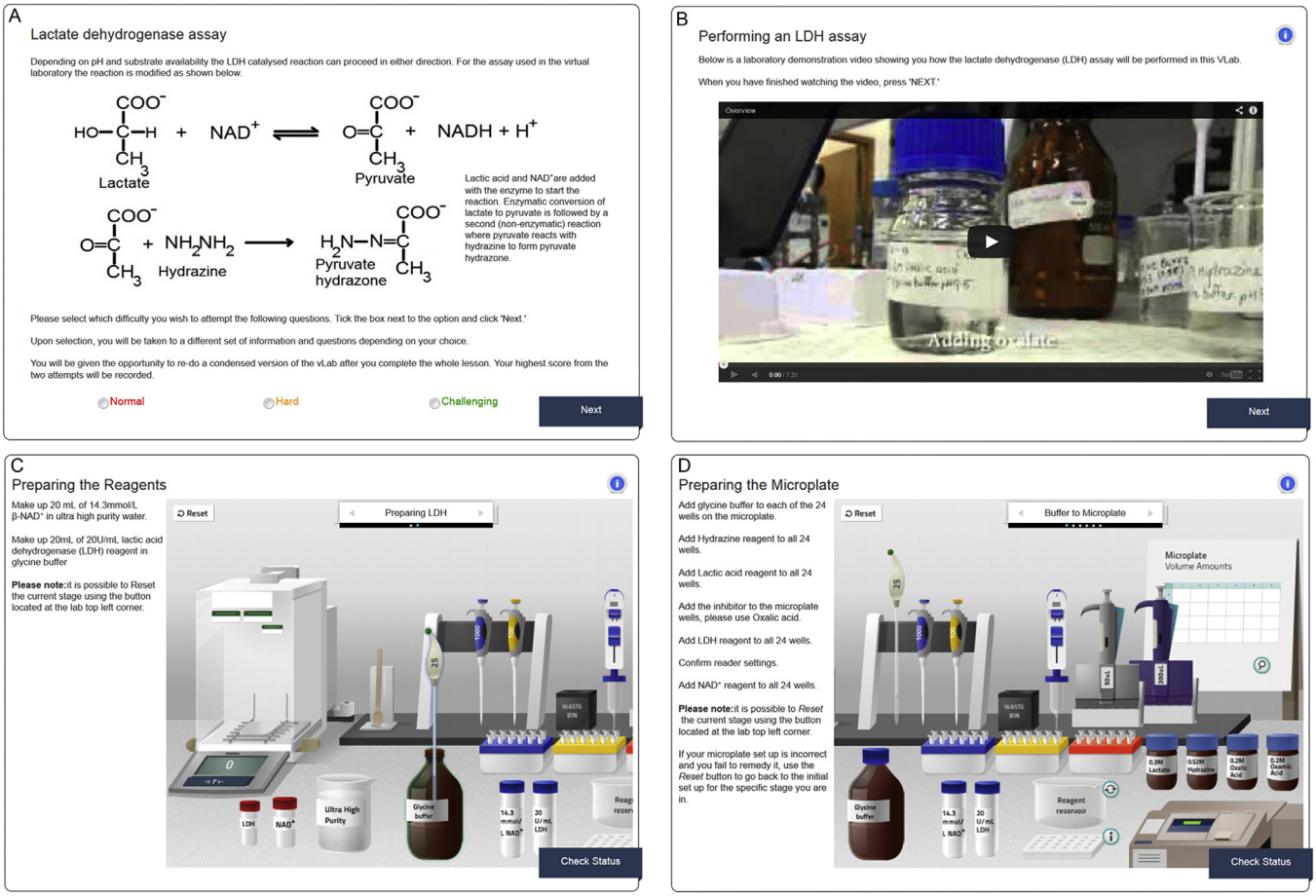

Fig. 2. Introduction and background components of vLab. (A) Screenshots showing learning objectives, general instructions, LDH reaction and biomedical importance. (B) vLAb simulation showing how to prepare reagents. Students read instructions and watch a video before preparing two key reagents. (C) Screenshot of another simulation where students get help to set up the assay in the microplate. (D) Using instructions, students pipette reagents into the 24-well microplate.

(2) Learning outcomes for the traditional classroom tutorial and the vLab were evaluated using 2 tests. All students completed a 10-question on-line quiz within 2 weeks (Fig. 4A) of the tutorial and 1 multi-choice question in their final exam paper, 2 months later (Fig. 4B). The online quiz included questions similar to those posed in the tutorial using kinetic data from the alcohol dehydrogenase-catalysed oxidation of methanol in the presence of ethanol. The final exam question used a reaction of the glycolysis pathway familiar to the students.

3. Results

3.1. Evaluation

The maximum possible LDH vLab score (using AeLP analytics) was 37. Student scores ranged from 1 (for a student who failed to complete the vLab) to 37. The average score was 19 ± 9 (SD).

Learning outcomes for the traditional classroom tutorial and the vLab were evaluated using 2 tests, 1 within 2 weeks (Fig. 4A) of the tutorial, and another, 2 months after the tutorial (Fig. 4B). Pertaining to Fig. 4A, the average score for the vLab group was 7.54 (±0.29 Standard Error), and that of the traditional classroom tutorial was 7.50 (±0.26 Standard Error). There was no statistically-significant difference ($P = 0.61$ from the Mann-Whitney U test) between the scores obtained by students who attended the traditional classroom tutorial, and those who used the vLab (Fig. 4).

3.2. Deployment of the vLab

A few students encountered technical problems from:

(1) high student load causing pages to load slowly
(2) students using old browser versions (despite detailed instructions)
(3) browser certificate problems on a few University of Tasmania (UTAS) computers
(4) occurrence of a system bug when "trigger-happy" students multiple-clicked certain screen icons
(5) few authoring errors
(6) incompatibility with iPad and tablets

A few students made complaints about incorrect scores but vLab analytics indicated the onus to be on those students. A few needed assistance with the use of the click-and-drag functions in the simulated laboratory. A few needed help to download the required (recent) browser versions. A few needed to be shown how to connect to UTAS Wi-Fi services.

3.3. Student learning outcomes from vLab use

Students were asked whether the vLab assisted their learning of major concepts (LDH enzyme kinetics). Thirty-five students provided feedback:

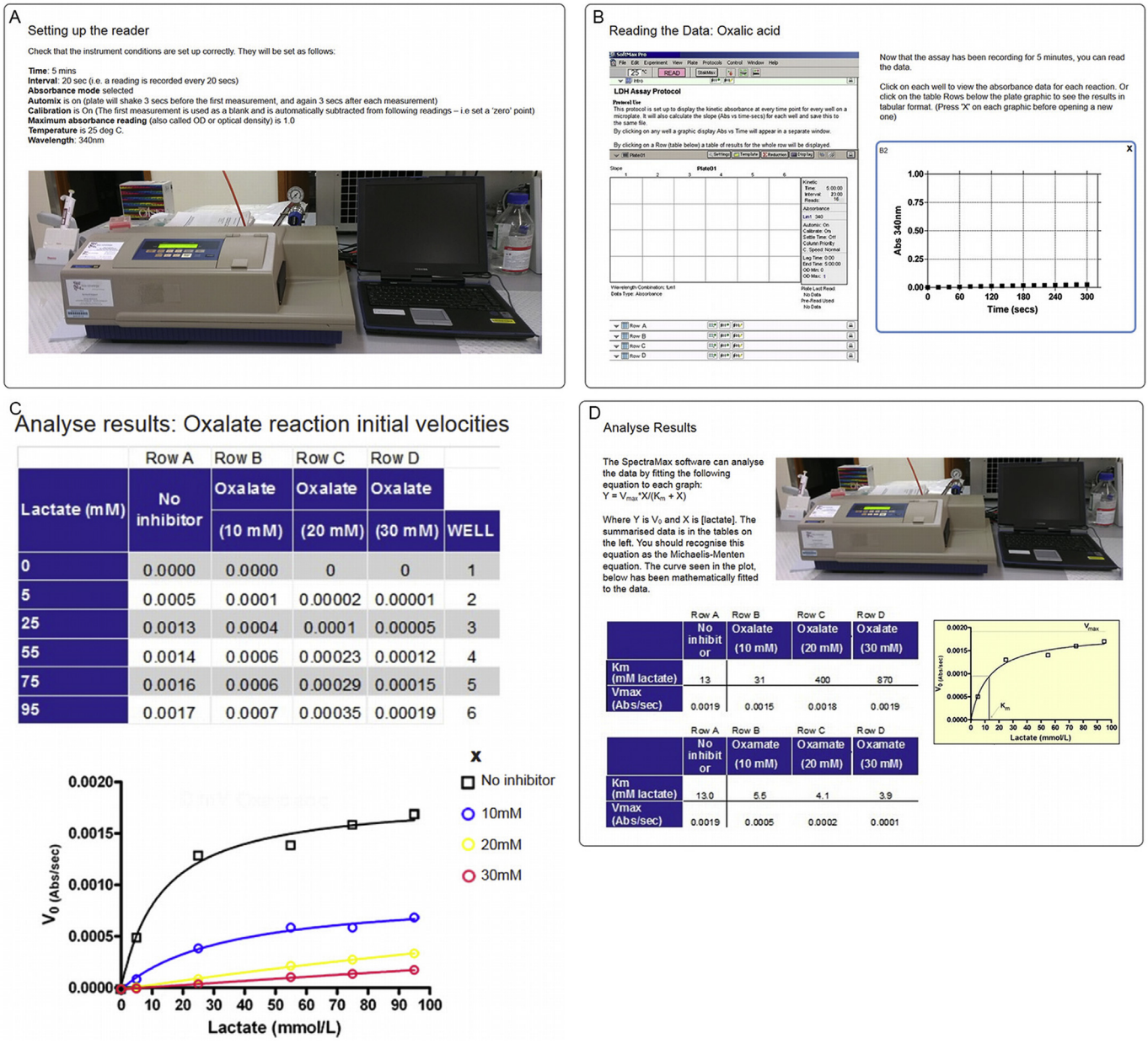

Fig. 3. Viewing of raw data and analysis of LDH kinetics results. (A) Microplate reader set up is illustrated with instructions for correct settings. (B) Students view the output from the microplate reader. (C) Initial rate velocities and enzyme function plots guided students through the analysis of results. Here, students were also given a chance to review concepts about enzyme structure and function. Graph-plotting software was used to calculate functional constants V_{max} and K_m. (D) Students are guided towards determining the type of enzyme inhibition.

- 7 found the vLab valuable
- 17 found the vLab somewhat valuable
- 11 opined that the vlab was of no value

3.4. Student assessment of vLab design

Students were asked to comment on the design of the vLab simulation. Thirty-five students provided feedback:

- 1 found the vLab extremely well-designed
- 16 found the vLab well-designed
- 12 opined that the vLab was of ordinary design
- 6 thought that the vLab was badly-designed

3.5. A few student feedback-vignettes on their vLab use

A few comments from our vLab student users include:

(1) "The e-learning questions were well constructed"
(2) "I liked the independent learning style and the ability to work at our own pace"
(3) "I prefer working with other students in a class situation"
(4) "The vLab was fun"

4. Discussion

We have described an adaptive vLab, not only for teaching LDH kinetics, but also for imparting the laboratory skills required to

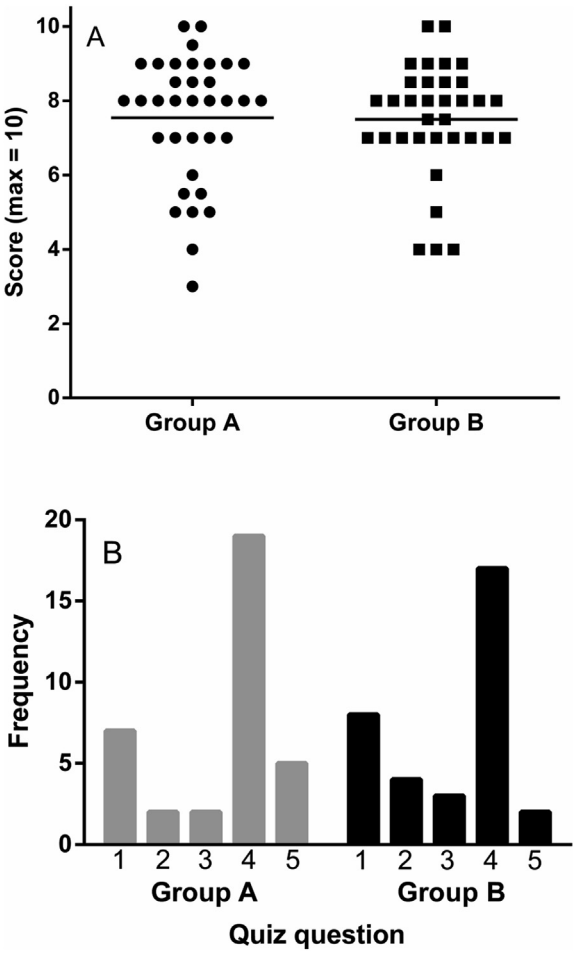

Fig. 4. Evaluation of student knowledge and understanding. (A) Students completed an on-line ten-question quiz within two weeks of the tutorial (Mann-Whitney *U* test; P = 0.61), and. (B) a multiple-choice question on the unit's final exam paper 2 months after the tutorial – 4 was the correct answer (Chi-square test; P = 0.68). In each case, there was no difference between the groups. Group A = vLab students (n = 35); Group B = classroom-based tutorial (n = 34).

perform the LDH assay. The student-responses data unequivocally rank the subject comprehension of LDH vLAb on par with a traditional classroom tutorial on the topic (Fig. 4). Some of the outcomes of this study are similar to those from another vLab study [15] using the Adaptive eLearning Platform (AeLP) developed by Smart Sparrow. That study entailed teaching Western Blotting to 3rd-year undergraduate science students undertaking a pathology course [15], in contrast to our study involving teaching lactate dehydrogenase(LDH) enzyme kinetics to 2nd-year biochemistry students.

The AeLP software platform [10,11,13,14] was pragmatically chosen because of:

(1) *Availability* – AeLP runs as we-based Software as a Service (SaaS), precluding the need for manual software-installation on student computers.
(2) *Ease of use* – The platform includes a What-You-See-Is-What-You-Get (WYSIWYG) author component, which includes a drag-and-drop interface used to design adaptive lessons in an intuitive manner.
(3) *Flexibility* – AeLP can be modified to facilitate various deployment types such as in-class/homework, private/public, and summative/formative feedback and assessment.
(4) *Adaptivity* – AeLP can be further adapted in response to tasks/questions and feedback/mistakes from students or colleagues.

We are currently engaged in overcoming the few technical hurdles encountered in our study, as posited in the "Deployment of the vLab" segment of the results section. We expect the student responses and uptake of vLAb will be substantially better with the revised version of the LDH vLab, using an improved deployment strategy.

Research on multimedia learning-aids demonstrate that multimedia presentations can result in deeper and more comprehensive understanding, as measured by problem-solving transfer, rather than single medium presentations [11]. The Cognitive Theory of Multimedia Learning (CTML) provides practical guidelines for designing animations in a way that promotes optimal cognitive processing and facilitates learning [16]. A major premise in CTML is that instructional messages should be designed in ways that minimise the chances of overloading the learner's cognitive system [11]. We designed the vLab to meet the 3 critical concepts undergirding CTML, namely; managing essential processing, minimising extraneous processing and facilitating generative processing [16].

Richard Mayer, in his book "Multimedia Learning" [11], discusses 12 cardinal principles/concepts that mould the attributes and efficacy of multimedia:

(1) *Coherence principle* – People learn better when extraneous words, pictures and sounds are excluded rather than included.
(2) *Signaling principle* – People learn better when cues that highlight the organization of the essential material are added.
(3) *Redundancy principle* – People learn better from graphics and narration than from graphics, narration and on-screen text.
(4) *Spatial contiguity principle* – People learn better when corresponding words and pictures are presented near rather than far from each other on the page or screen.
(5) *Temporal contiguity principle* – People learn better when corresponding words and pictures are presented simultaneously rather than successively.
(6) *Segmenting principle* – People learn better from a multimedia lesson is presented in user-paced segments rather than as a continuous unit.
(7) *Pre-training principle* – People learn better from a multimedia lesson when they know the names and characteristics of the main concepts.
(8) *Modality Principle* – People learn better from graphics and narrations than from animation and on-screen text.
(9) *Multimedia Principle* – People learn better from words and pictures than from words alone.
(10) *Personalization Principle* – People learn better from multimedia lessons when words are in conversational style rather than formal style.
(11) *Voice Principle* – People learn better when the narration in multimedia lessons is spoken in a friendly human voice rather than a machine voice.
(12) *Image Principle* – People do not necessarily learn better from a multimedia lesson when the speaker's image is added to the screen.

The vLab conforms to these principles of educational technology [11] in manifold ways:

(1) The animation per se includes minimal text resulting in retrenching burdensome cognitive load [16,17].

(2) The visual elements, synchronised with text within the animation, promotes temporal contiguity [18,19].
(3) The coherence principle is supported when error messages appear in response to the learner's mistakes [20].
(4) Spatial contiguity is enhanced by placing text on or next to the objects in the virtual laboratory stage [19,21].
(5) The high level of interactivity in the vLab facilitates generative processing [16,22].

We have therefore successfully designed a new web-based e-learning method to teach enzyme kinetics and laboratory skills needed for the LDH assay. This new approach categorically improved learning outcomes, outcomes on par with a traditional classroom tutorial. Learners controlled the order, pace and other interactive elements of both the tutorial and the animation. This graduated learning experience accommodated the expertise-accruements during the biochemistry vLab class, which in turn, maintained/promoted commensurate interest from these students users [23]. Our novel adaptive vLab is therefore a useful, economical, and attractive resource for teaching LDH kinetics.

5. Conclusions

We confidently posit online laboratory simulations as an expedient, time-efficient and cost-effective approach to teaching laboratory science. Cost issues pertaining to expensive reagents, and safety issues related to hazardous chemicals can be conveniently obviated. Online laboratory simulations can assist students from the outback to familiarise themselves with laboratory procedures before they attend sessions on their enrolled academic campus [4]. When simulations are integrated with other educational activities [11], they promote learning. Simulations may assist revision of laboratory work whilst students are away from their academic campus of involvement. Since the academic utility of our new adaptive vLab simulation of LDH kinetics was amply demonstrated, the same principle can be extended to a number of other experiments, especially ones that involve complex methods and/or hazardous chemicals.

Ethical approval

This study was approved by the University of Tasmania Human Research Ethics Committee.

Authors' contributions

CB – Christine Booth – Study design, study execution, data collation.

RC – Rajkumar Cheluvappa – Data collation, data analysis, manuscript drafting, manuscript editing, manuscript submission, *de facto* correspondences.

ZB – Zack Bellinson – Software design, software programming.

DM – Danni Maguire – Software design, software programming.

CZ – Craig Zimitat – Study design, study execution.

JA – Joyce Abraham – Analysis of IT information (Software life cycle, Software quality assurance analysis).

RE – Rajaraman Eri – Study design, study execution, *de jure* correspondences.

Conflicts of interest

None.

Guarantor

Rajaraman Eri, Rajaraman.Eri@utas.edu.au.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.amsu.2016.04.019.

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