Follow the Glucose Molecule: Learning Pharmacology by Exploring Multi-Scale Agent-Based Computer Models of Cellular Biochemical Processes and their Interactions Between Organs

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Abstract

This paper presents the Pharmacology Inter-Leaved Learning-Cells (PILL-Cells) environment. This is a suite of multi-scale agent-based computer models that enable nursing students to investigate the biochemical processes of diabetes and its related medications. These range from the molecular to the cellular to the interactions between organs within a sick or healthy cell-organ. The participants were nursing students who learned about the pharmacology related to diabetes either with computer models (experimental group; n = 94) or via a lecture-based curriculum (comparison group; n = 54). The results revealed significantly higher conceptual learning gains following learning with the PILL-Cells environment compared to studying via the lecture-based curriculum ($U = 940$, $p < 0.001$). It was found that the highest conceptual learning gains were for the medication treatment subscale and the highest complex systems learning gains were at the micro-level. These results suggest that learning with the PILL-Cells is highly effective and enhances a micro-level molecular view of the biochemical phenomena, and that this understanding is then related to macro-level phenomena such as medication actions. Additionally, the scores of the course final exam were higher in the experimental group (unpaired $t = -2.9$, $p < 0.05$), which suggest that the environment continues to provide a more general reasoning scheme for biochemical processes, and thus enhances the pharmacology curriculum.

Keywords: Complex-systems, Model based learning, Nursing education, Medical education, Pharmacology.

Introduction

This paper presents the Pharmacology Inter-Leaved Learning-Cells (PILL-Cells) environment (Dubovi, Levy & Dagan, 2014) that enables nursing students to learn biochemical concepts related to diabetic drug actions. In order to enhance nursing students' conceptual understanding of pharmacology, which is necessary for self-monitored practice in medication administration, we have designed agent-based computer models of multi-level biochemical processes of diabetic drag action. The diabetic topic was chosen due the complexity in the nature of the disease in the molecular level, the organs involve and the metabolic mechanisms in the body, consequently, is required a complex care management and intensive follow-ups. PILL-Cells environment is designed as part of a larger educational architecture aimed at addressing the problem of bridging the gap between theory and practice in academic teaching of practical professions.

Literature-Review

Pharmacology education

Registered nurses are the primary practitioners responsible for the preparation and administration of medication and spend between 21-40% of their time on this task (Westbrook et al., 2011). As medication managers, nurses have to prepare and calculate the right dose, assess the appropriateness of the medication for a particular patient, identify errors, administer via the correct route, monitor and evaluate the medication effect, and educate the patient on the drug's effectiveness and possible side-effects (Choo et al., 2010). Nurses are at the front-line of the medication management chain, administering approximately 7000 medications doses daily in a typical national hospital. Hence, the pharmacology education should be effective and prepare nurses to carry out these tasks in an informed and safe manner. Pharmacology lecture-based courses traditionally include the following topics: generic drug names and classes, indications of use, normal dosages, pharmacokinetics ("Pharmacokinetics is the study of drug concentrations during the processes of absorption, distribution, biotransformation, and excretion" (McKenry, Salerno & Hamelink, 2006, pp. 36)). It is common to define these interactions as actions of the body on the drug) and pharmacodynamics (Pharmacodynamics is the study of interactions with specific macromolecular components in tissues, typically receptors (McKenry et al., 2006). It is common to define these processes as actions of the drug on the body), therapeutic effects, side effects, food or drug interactions, and the medication process. Safe and effective pharmacotherapy is strongly based on the basic science concepts of the relevant physiology, anatomy, pathology and microbiology (Banning & Cortazzi, 2004).

Unfortunately, several studies have suggested that often nursing curricula do not supply the required foundation of knowledge to undertake drug administration effectively with nurses having inadequate knowledge of pharmacology (Meechan et al., 2011; Ndosi & Newell, 2009). Nurses and nursing students generally find that pharmacology is interesting but difficult, self-rating their pharmacology skills as low, especially for pharmacokinetics and pharmacodynamics, a crucial component in understanding how drugs and bodies interact. Studies have described the traditional educational approach as causing "confusion, disinterest, inattentiveness… culminating in underachievement and poor learning outcomes" (Dilles et al., 2011; Charles & Duffull, 2001, pp. 396). There are very few studies which have aimed at enhancing nursing students' conceptual knowledge of pharmacodynamics and pharmacokinetics (Meechan et al., 2011). Additionally, learning with computerized models has not been documented in the nursing and medical education literature. Here we present a multiscale model - molecular to cellular to organ interactions - with a complex systems approach which aims at enhancing the understanding of diabetic medication mechanisms, actions and interactions.

Conceptual understanding through the lens of complex systems

The domain of complex systems has evolved rapidly in the past 25 years with the development of novel ideas and tools, and new ways of comprehending phenomena via computer science, biology, economics, physics, chemistry and many other fields. Complex systems are comprised of sub-micro-level elements (often referred to as "agents"), which interact with each other and with their environment. The interactions of numerous submicroscopic elements result in a higher-order or collective behavior; a macro-level phenomenon. Such systems are emergent; although they are not regulated through a central control, they self-organize in coherent global patterns (Holland, 1995; Kauffman, 1995).

A pharmacological process is a prime example of a complex system. Many different interconnected molecules interact with one another and with drug molecules (pharmacodynamic processes) and with normal body processes (pharmacokinetic processes) that lead to the emergence of therapeutic or toxic effects (Katzung et al., 2012). These pharmacodynamic and pharmacokinetic nonlinear interactions are unique for each medication and vary between different patient clinical states. Pharmacological processes become more complex when patients are treated by several medications and/or suffer from multiple morbidities.

This study builds upon previous research on the value of models for learning science, by extending it to understanding how models based on a complex systems perspective may support pharmacology learning. Here we use Agent-Based Modeling (ABM) which creates an explicit causal link between the micro-level elements of a system and its macro-level global behavior, which in this study aids students' understanding of a drug's global behavior from its actions at the micro-level for the global behavior, macro-level. ABM was first used in computer models in social science and ecology, but has since been applied to a wide range of biological problems in recent years, particularly for modeling pathophysiological processes with a significant spatial component (An & Wilensky, 2009; Bhattacharya et al., 2012). NetLogo (Wilensky, 1999) is one such modeling environment. NetLogo is a widely used general-purpose agent-based (open-source) modeling language that enables exploration and construction of models of complex systems (http://ccl.northwestern.edu/netlogo). In this study, NetLogo was used to construct multiscale models of an organ's cells and molecules.

Research aim

The purpose of this study was to design and evaluate the effectiveness of multi-scale agent-based computer models to teach nursing students pharmacology, specifically, diabetes molecular and somatic mechanisms and treatment related medications.

Methods

Pharmacology PILL-Cells environment

The PILL-Cells environment was constructed with the NetLogo modeling language. The PILL-Cells environment consisted of multiscale models of an organ's cells and molecules to model the metabolic processes and medication mechanisms in the blood glucose level equilibrium. In this way, the models explained body functioning during health and disease and the body's reaction to medications. The students were able to simulate a sick cell organ and patient (diabetes mellitus type 1 or type 2) and then add different doses of medications, manipulate a patient's characteristics and habits (such as fasting or sport activity), and observe the subsequent body reaction.

Two central representations were used (Figure 1). The first representation was comprised of physical agent-based models of the relevant anatomy: a) *Pancreas cell*s – alpha-cells which are responsible for glucagon secretion and beta-cells which are responsible for insulin secretion; b) *Muscle cells* which use glucose for glycolysis (the pathway for producing ATP or energy) which is mediated by insulin; c) *Liver cells* which store glucose as glycogen and then allow the breakdown of glycogen (glycogenosis) when blood glucose is low. The multi-scaling enables students to zoom-in on each type of cell separately or to zoom-out on the four different types of cells altogether for a more comprehensive exploration of the glucose equilibrium. This ability to manipulate the model and explore various aspects easily and repeatedly enables students to relate the biochemical reactions and glucose equilibrium to both the relevant anatomy and physiology and to different medications and patient behaviors. The second central representation was comprised of graphs of the amount of insulin, glucose and medication molecules in the various relevant body parts.

Exploration of multi-scale cell models supports a mechanistic view of the system, while exploration of the graphs affords understanding of the general disease process, in this case, the quantitative aspects of diabetes and its medication over time. Thus, the students can relate the interactions between medication molecules and the body's cells with the body's global behavior in terms of pharmacokinetics and pharmacodynamics.

Worksheets were part of the learning environment to guide activities, provide information and ask questions.

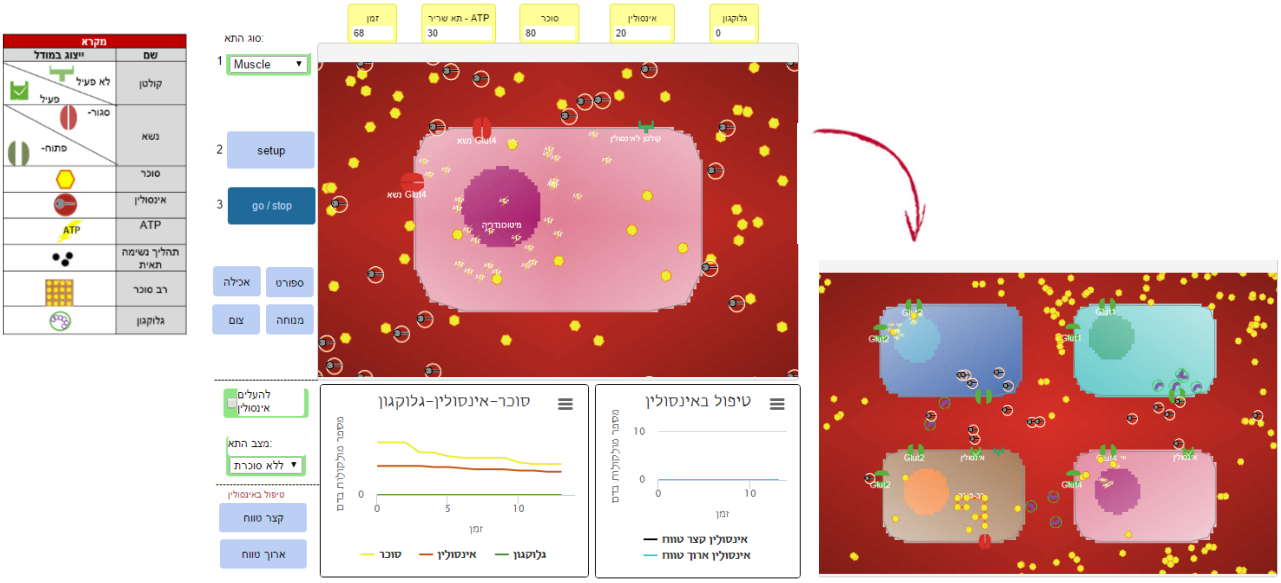

Figure 1. The PILL-Cells environment which is a suite of multi-scale molecular, cellular and organ interaction models within the sick or healthy cell organ. With agent-based computer models the students can investigate the biochemical multi-level processes of medications. The students can zoom-in on one cell type or zoom-out on the four cell types which are responsible for glucose equilibrium.

Research design

We conducted a controlled quasi-experimental pre-test-intervention-post-test design using a quantitative approach. The current study was based on the initial design of agent-based computer models that we developed in early 2014 (Dubovi et al., 2014).

Participants and Procedure

Participants included volunteer sophomore nursing students ($N = 148$) who were attending a traditional lecture-based pharmacological course that totals 56 hours (14 weeks) of teaching during the fall semester.

The study comprised two groups of students: 1) the comparison group ($n = 54$) who received teaching via the diabetes pharmacology lecture-based curriculum for a total of four hours, and 2) the experimental group ($n = 94$) who received teaching via diabetes pharmacology computer models for approximately 3-4 hours. Pre- and post-test evaluations were undertaken at the beginning and at the end of the semester (nearly two months before and one month after the activities on the last day of the semester).

There were no statistically significant differences in demographic characteristics and baseline academic achievements between the experimental and the comparison group (Table1).

Table 1. Demographic Characteristics and University Entrance and Course Achievements: Comparisons between the Experimental and Comparison Student Groups

	Total (N=148)	Experimental Group (n=94)	Comparison Group (n=54)	Statistics[1]
Age (years)	23±3	22.9±2.8	22.7±2.3	0.50 (p = .62)
Female	110 (74)	69 (73)	41 (76)	0.20 (p = .43)
Male	38 (26)	25 (27)	13 (24)	
Jewish	47 (32)	32 (34)	15 (28)	1.2 (p = .73)
Christian	29 (20)	20 (21)	9 (17)	
Muslim	60 (40)	36(39)	24 (44)	
Druze	10 (7)	5 (5)	5 (9)	
Other	2 (1)	1 (1)	1 (2)	
Psychometric Entrance Test score[2]	626±43	604±49	594±41	0.28 (p = .77)
Hebrew (YAEL test) score[3]	115±12	113±12	116±10	–1.36 (p = .17)
Chemistry course score	70±24	67±16	75±34	–1.9 (p = .07)
Microbiology course score	87±9	88±8	86±8	0.74 (p = .45)
Cell-biology course score	91±8	91±8	91±8	0.35 (p = .75)
Biology course score	90±9	91±8	89±10	0.58 (p = .6)

Numbers represented N (%) or Mean±SD

[1] Based on Chi square test or independent sample t-test appropriate

[2] Psychometric Entrance Test is a standardized test in Israel, generally taken as a higher education admission exam. It covers three areas: mathematics, verbal reasoning and English language.

[3] The YAEL test is a Hebrew proficiency test. Students who take the Psychometric Entrance Test in any language other than Hebrew are also required to take the YAEL test. Here we report the mean scores of 27 students in the comparison group and 50 in the experimental group who took the YAEL test.

Data collection instruments

Pharmacology-diabetes questionnaire

The pharmacology-diabetes questionnaire consisted of 14 multiple-choice questions and was developed specifically for this study. The items were validated by experienced lecturers in our nursing department to ensure appropriate context- and content-alignment and a suitable level of expertise. A two-dimension analysis of all questions was conducted: One dimension described a conceptual pharmacology content which was divided into three sub-scales of pharmacology-diabetes medications: (1) Glucose equilibrium; (2) Diabetic disease; (3) Medication treatment (Appendix A); The second dimension involved complex system components: (1) Micro-level of the system; (2) Macro-level of the system.

Analysis of the pharmacology-diabetes questionnaire using Cronbach alpha yielded an internal consistency score of .71.

Course final exam

The course final exam consisted of 40 questions related to the basic principles of pharmacology organized according to body system or disease medication treatment. The exam was written and validated by course lecturers.

Demographic questionnaire

A demographic questionnaire comprised information about the participant's gender, age, religion and previous work experience in health organizations.

Statistical analysis

The responses from the pharmacology-diabetes questionnaire were coded as correct or incorrect, and the total score was calculated as the percentage of correct answers. The questionnaire was analyzed for two dimensions: pharmacology concepts and complex system components. The pre- and post-test results were analyzed with descriptive statistics (Mean, SD and Median). Gained knowledge following learning with computer models was also calculated as [(post-test score) – (pre-test score)]/(pre-test score). These scores were compared using a Mann-Whitney U test for non-parametric data with an effect size as r (Fritz, Morris & Richler, 2012).

The preliminary analyses of final exam scores were compared using unpaired t-tests.

Results

The students' pharmacology-diabetes questionnaire results for pharmacology concepts and complex system components are shown in Table 2. The learning gains for the experimental group were significantly higher than for the comparison group for both the pharmacology concepts and complex system components with a medium-high effect size. When looking at the questionnaire subscales, for the pharmacology concepts dimension, the highest learning gain was the medication treatment, while for the complex system dimension, the micro system component subscale had the highest learning gains.

The preliminary analysis of the course final exam revealed significant lower scores in the comparison group compared to the experimental group ($M = 68$, $SD = 15$ versus $M = 75$, $SD = 14$, respectively; unpaired $t = –2.9$, $p < 0.05$; Figure 2).

Table 2. Comparisons of Pre-test and Post-test Pharmacology- Diabetes Questionnaire Scores and Learning Gains between the Two Student Groups (N=148)[1]

	Pre-test Scores		*Post-test Scores*		*Learning gain* [2]		*Statistical tests*	
	Exp. (n=94)	*Comparison* (n=54)	*Exp.* (n=94)	*Comparison* (n=54)	*Exp.* (n=94)	*Comparison* (n=54)	*Mann-Whitney U*	*Effect size, r*
Pharmacology-Diabetes Concepts, Overall: Subscales:	34±17	30±17	73±14	36±23	153±148, *Mdn.*=100	26±101, *Mdn.*=0	940***	0.53
Glucose equilibrium	16±25	11±23	64±39	17 ±27	54±55, *Mdn.*=50	1±45, *Mdn.*=0	1036***	0.50
Diabetic disease	51±37	40±38	88±23	50±37	56±51, *Mdn.*=100	16±51, *Mdn.*=0	1417***	0.34
Medication treatment	35±22	36±24	70±17	39 ±29	92±88, *Mdn.*=75	0±69, *Mdn.*=0	1077***	0.48
Complex Systems Components:								
Micro	30±23	26±22	75±23	34±29	96±100, *Mdn.*=100	19±82, *Mdn.*=0	1173***	0.45
Macro	39±24	34±22	72±16	38±32	82±82, *Mdn.*=50	19±105, *Mdn.*=0	1422***	0.34

Exp = experimental group; Comparison = comparison group

[1] Data are presented in percentage mean ± SD, Mdn = median, Range 0-100

[2] Learning gains were computed to take into account differences in prior knowledge before learning with computer modules: (post-score – pre-score)/(pre-score), i.e. the proportional change from baseline initial understanding.

*** $p < .001$

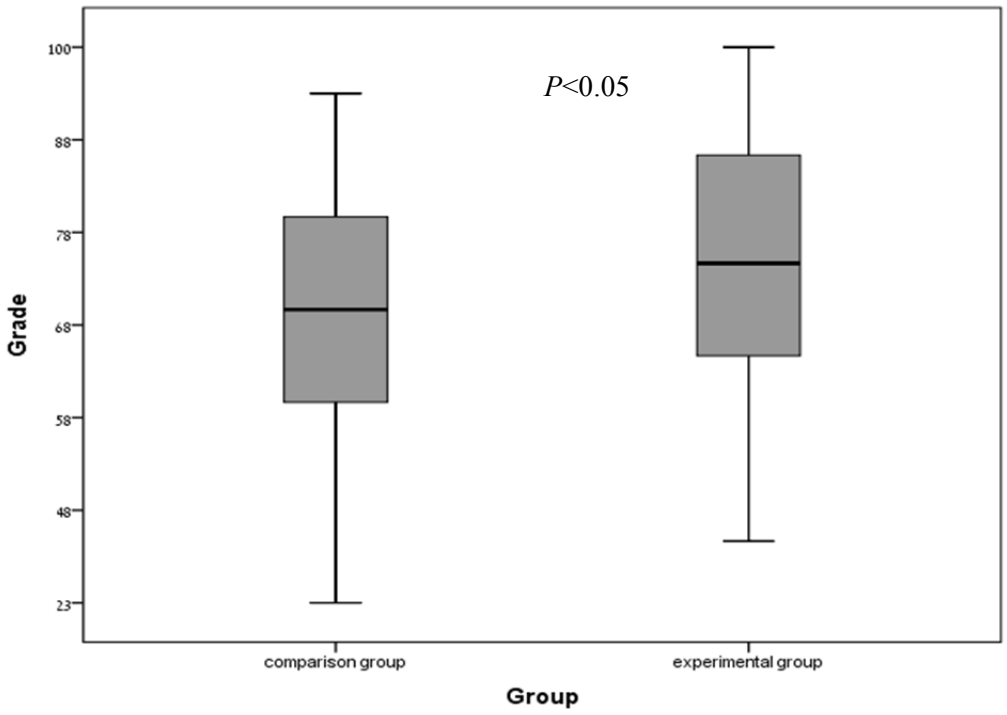

Figure 2. Comparison of course final exam scores between the comparison group which learned with a lecture-based curriculum and the experimental group which learned the diabetic related pharmacology within the PILL-Cells environment.

Discussion

This study supports the benefits of using the PILL-Cells environment as a teaching strategy in the pharmacology education of nursing students. We have shown that among complex system components, the main benefit for the experimental group was at the micro-level, while, among pharmacology concepts, the medication subscale had the highest learning gains. Hence, learning based inquiry at the micro level of molecules and cells, can enhance the understanding of the macro biochemical phenomena such as the pharmacokinetics and pharmacodynamics of medications. Similar advantages of agent-based modeling which bring micro- and macro-levels closer have been shown in previous studies of learning (for example, Levy & Wilensky, 2009). The present study contributes to the professional education field by suggesting that an ABM is a powerful tool for integration of the basic science concepts and practically related concepts, such as pharmacology. Additionally, we found evidence of an extension of this learning to other topics in pharmacology as shown by the heightened scores of the course final exam above and beyond the learning gains about diabetes.

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Appendix A

Example of three questions from the pharmacology-diabetes questionnaire:

Example 1

Arrange the order of the various mechanisms which are responsible for insulin secretion from beta cells in the pancreas:

__During cellular respiration, ATP is produced
__Calcium channels open
__Calcium molecules enter the cell
__The level of insulin secretion rises
__Glucose enters the cell
__Potassium channels close

Correct answer: Glucose enters the cell**;** During cellular respiration, ATP is produced**;** **Potass**ium channels close**;** Calcium channels open**;** Calcium molecules enter the cell**;** The level of insulin secretion rises.

Example 2

Jonathan has diabetes type 1. Before he starts playing basketball, he should:

a. Inject short-acting insulin
b. Eat an energy bar
c. Continue as usual
d. Not engage in sport activities
e. I don't know

Please explain your answer. Describe how physical activity influences the interaction between glucose molecules and cells.

Correct answer: b

Example 3

A patient is fasting from midnight to prepare for surgery. During the morning shift you receive a physician order to administer to the patient T. Glibenchlamide (Gluben 5 mg). What should you do:

a. Check his blood glucose level and if it is OK, administer the medication
b. There is no need to administer the medication because the blood glucose level in the morning tends to be high
c. Monitor the blood glucose level, but without administering the medication during fasting
d. Monitor the blood glucose level, and ask the physician to change the order to a short-acting insulin treatment
e. I don't know

Correct answer: c