Educational Visualization of Cell Processes

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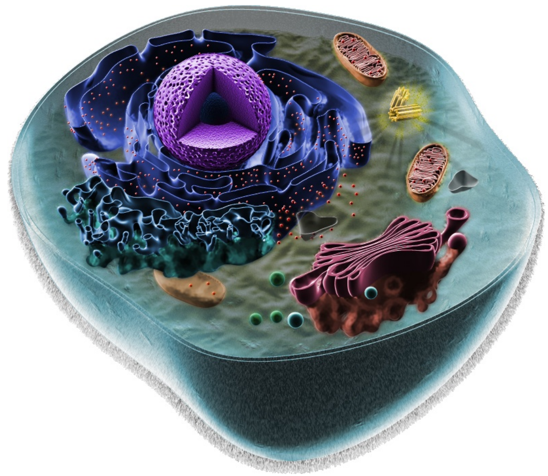

Figure 1: Rendered cell

Abstract

Educational visualizations prove to have a major enhancing impact on the educational process. Especially for complex topics like microbiological cell progresses such techniques can prove incredibly useful. In order to fulfill the high standards of educational materials however, visualizations need to be presented in a motivating way. For this purpose, educational games could be a practical solution. To help those games sustain a high motivational level, different theories have been created.
In order to accomplish a structured overview for this paper, a theoretical basis on cell biology is given first. Afterwards the state of the art techniques of visualization on a microbiological scale are presented and discussed (figure 1 [1] shows an example of a rendered cell). Subsequent to the theoretical visualization part, the circumstances in the video game industry will be presented. Afterwards the theoretical basis of educational games will be discussed and difficulties within this emerging field will be presented. Finally a conclusion summarizes the effort made into identifying the challenges of developing such a game.

Keywords: visualization, cell, cell processes, samples, microscopy, tomographym light microscopy, video games, serious games, educational games, entertainment education concept, ARCS-model, flow, game based learning cycle, requirements characteristics, game quality indicators, learner modelling, cellcraft, spore, thrive

1 Introduction

With the capitalization many new forms of computational sciences came available and beared different benefits as well as drawbacks. One emerging field that emerged out of this development is known as ”visual computing” and refers to handling with images and 3D models and their data. This term includes for example disciplines like computer graphics, image processing, visualization, computer vision and pattern recognition. Visual computing is especially valuable in fields of application like medicine or biology due to the massive enhancement of comprehensibility for not only physicians but also students. Especially the visualization of cellular structures and processes still suffers from massive restrictions due to the scale of the structures. Modern biology knows a variety of different ”organelles” within biological cells, but is still capable of understanding only a fraction of the processes that happen within the body and the cells. Visual computing offers a great opportunity to picture scenes and data that normally operate on a scale that would not allow scientists to observe processes visually while they get executed.

Visualization progresses and solutions found quite elaborate applications in disciplines like in medicine, entertainment or business and management over the last decades. Applications of visualization that deal with the visualization of biological structures, like cells, are still quite unusual in educational process. Particularly games have been emerging during the last 2-3 decades as an useful application for such educational purposes. Terms associated to the process of embedding video games into daily

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[1] http://www.discoveryexpresskids.com/uploads/2/5/6/9/25695369/643414263.jpg

life tasks like ”gamification”, ”serious games” or ”educational games” are gaining increasingly popularity. This process is due to the fact that these educational games bear huge benefits for different task sets. Games are for example: adaptable, motivating, exciting, simplistic, ... These characteristics are especially suitable if such educational games deal with rather complex subjects, like biological constructs. Due to the high complexity of processes within the human body it is rather elaborate to teach children and young adults the exact structure of organisms on a cellular basis.

However there are plenty somewhat difficult task to manage prior to developing an educational game. This article will cover most of the basic assumptions, thoughts and difficulties on developing an educational visualization (game) about cell processes.

2 Cell biology

To give a non-biologist an overview of the cell biology and to understand what is so special about it, the following chapter presents the basics, types, structure of the cell and how it basically works. For a better understanding of the cell and biology in general, further reading in corresponding literature is recommended. The following information should give an impression that not every cell is equal and that there are a lot of small differences between them.

2.1 Basics

In the dictionary of cell and molecular biology the cell is defined as:

> *An autonomous self-replicating unit (in principle) that may constitute an organism (in the case of unicellular organisms) or be a subunit of multicellular organisms in which individual cells may be more or less specialized (differentiated) for particular functions. All living organisms are composed of one or more cells. Implicit in this definition is that viruses are not living organisms and since they cannot exist independently, this seems reasonable.* - [Lackie 2013]

Therefore a cell is the smallest living unit. These units can bind themselves to create organisms in which some cells change their function to specialize on something. An animal or human contains multiply hundred of such cells. Mostly this specialized cells lost their ability to live on their on, so they need each other so survive. There are two main kinds of Cells, the eukaryotes and the prokaryotes which differ in their internal structure and their organelles.

2.2 Prokaryotes

Figure 2 shows a schematic picture of a prokaryote. This unicellular organisms were the first form of life on earth and are characterized by the possession of one or more simple DNA chromosomes, usually circular. They are self-sustaining and are in comparison to the eukaryotic cells simpler, smaller, without a nuclear membrane and only possesses a very small range of organelles. [Beginnen et al. 2005]

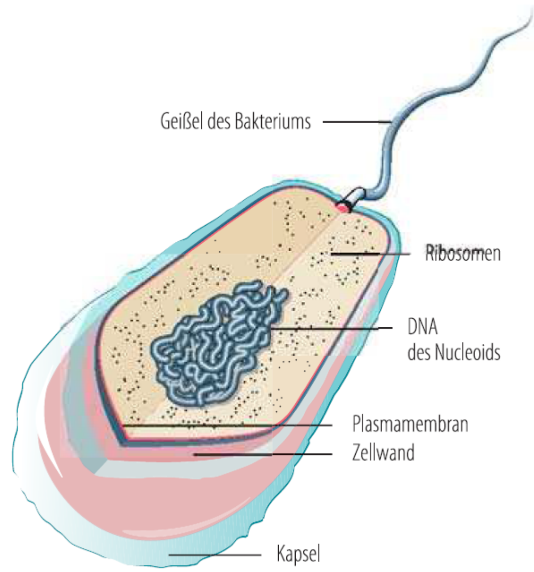

Figure 2: Prokaryote cell
[Beginnen et al. 2005]

2.3 Eukaryotes

Eukaryotes are one of the major subdivisions of living organisms and can be divided in three more sub-types. These types are the plant-, animal- and fungus-cells. Figure 3 shows a plant cell and figure 4 shows an animal cell. The three types have some shared properties but also many differences.

The eukaroytic cells have linear DNA organized into chromosomes with with nucleosomal structure involving histones (highly alkaline proteins). The nucleus is separated from the cytoplasm by a two-membranes and partition of various functions in some distinct cytoplasmic organelles. There are also a range of other characteristics which distinguish the eukaroytic cells from the prokaryote cells. Section 2.4 and section 2.5 shows most of them. distinguish them from the prokaryotes. [Beginnen et al. 2005]

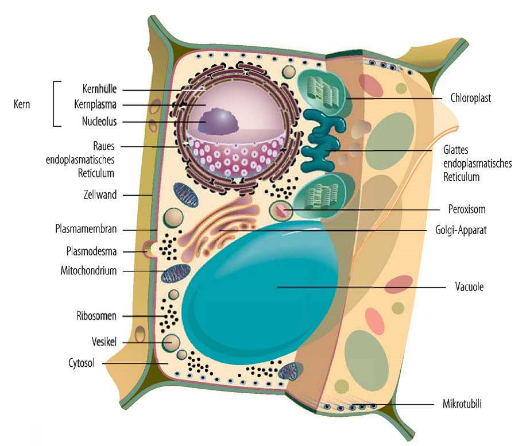

Figure 3: Plant cell
[Beginnen et al. 2005]

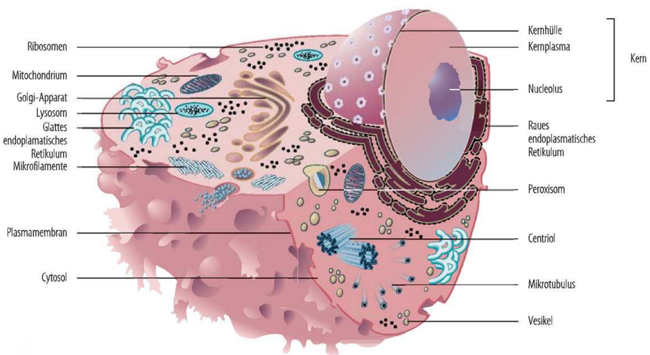

Figure 4: Animal cell
[Beginnen et al. 2005]

2.4 Shared Characteristics

- Similar membranes
- For the genetic information in the DNA the same genetic code is used
- Similar mechanism for the transcription and translation of the genetic information
- Same metabolism
- Same energy saving
- Same photosynthesis-mechanism (plants)
- Same way of recycling proteins

2.5 Eukaryotes Characteristics

- Nukleolus and cytoplasma are separated
- Mitoses
- More complex Organelles
- Specialiced organelles for aerobe breathing (mitochondrium) and photosynthesis
- Complex cytoskelton
- Reproduction through meiosis
- Existance of three different RNAs
- Two gencopies per cell
- Cell wall contain cellulosis (plants)
- Complex flagella and fimbria

2.6 Structure of cells

Every cell, whatever prokaryotic or eukaryotic, has a cell membrane, which divides it from the environment. This cell membrane is it which controls what goes in and out of the cell. On every side of the membrane are ions (loaded atoms or molecules) with different concentration. The use of this difference between the concentrations is to keep the membrane up. Within the cell membrane, the cytoplasma and all organelles are located. Every cell which is able to divide itself posses DNA, in which the genetic information is saved. In addition to the DNA proteins are saved. This proteins are used as catalysts for some enzyme reactions or for building up structures inside the cell. The following points make a basic explanation what the components of the cell are: [Beginnen et al. 2005]

- **Cell membrane** - divides it from the environment, protects the cell and is responsible for what goes in and out of the cell
- **Cytoskeleton** - defines the shape of the cell, but also is very dynamic and adaptable
- **DNA / RNA** - deoxyribonucleic acid / ribonucleic acid are the two kinds of genetic material in a cell. It is used to save information in the long term. The cell needs it to grow, develop, function and reproduce - the building block of life.
- **Flagellum** - structure to allow movement for bacteria, archaea and eukaryote
- **Ribosome** - are consisting of RNA and are responsible for protein synthesis in a cell
- **Centrioles** - are cylindrical shaped protein structures needed for the mitoses and provides stability to the cell. Centrioles does not are common in higher developed plants.
- **Organelles** - are the smaller parts of organs in cells in comparison to the organs in higher developed animals like humans. The following organelles are the most important:

  Cell nucleus contains chromosomes composed of DNA and is enclosed within a membrane (at least in eukaryotic cells). It is the central control organelle of a cell

  Mitochondrion are the factories of cell and are found in almost all eukaryotic organisms. Their major task is to produce energy. They do so by releasing energy in the form of ATP

  Plastid - are only existing in plant-cells and are responsible for photosynthesis

  Endoplasmic reticulum and Golgi apparatus - these two organelles are tight functional connected. The ER is responsible for translation, protein-folding, transporting chemical elements and proteins. The golgi apparatus distributes the proteins and eventaully modifies them.

  Lysosome and Peroxisome are the digestion organelles of a cell

  Vacuole stores materials, cell sap and is maintaining hydro-static pressure and acidic internal pH. It is also the exporting organelle of a cell to get rid of unwanted substances.

3 Visualization

This chapter describes step by step how a biological cell gets analyzed, segmented and finally rendered. It starts with a brief overview about the whole process and then some ways to obtain information of cells and at last how to get a visualized picture from the sample data.

Over the past decades microscopy of cells has changed a lot. So has the image analysis, from hand drawing and photographs to computational methods that automatically or at least semi automatically quantifies objects and other specification of interest. Nowadays the imaging technologies generate a huge amount of data, even multi-dimensional. The outcome is a lot of qualitative data. The next thing is to proceed this qualitative data to quantitative values. This values build up the basics for mathematical modelling of proteins and biochemical signal networks. [Eils and Athale 2003]

Cells are very small and complex, therefore it is not easy to see their structure, their molecular composition and hard to find out how their various components work, even with an microscope. Light and electron microscopy allows to study the basic structure and function, but no single microscopy technique is capable to extract all information out of a cell. To learn better from the cell, many tools and techniques have evolved. The introduction of these has lead to major advances in cell biology. To achieve the best results, it is recommended to use multiple imaging modalities, spanning a range of scales and frequencies. If possible it should be executable without destroying the cell. This is mostly not easy to achieve but with the preservation of the hydrated nature of the cell, features of interest can be capture with a higher-resolution. [Plitzko et al. 2009] [Uzman 2003]

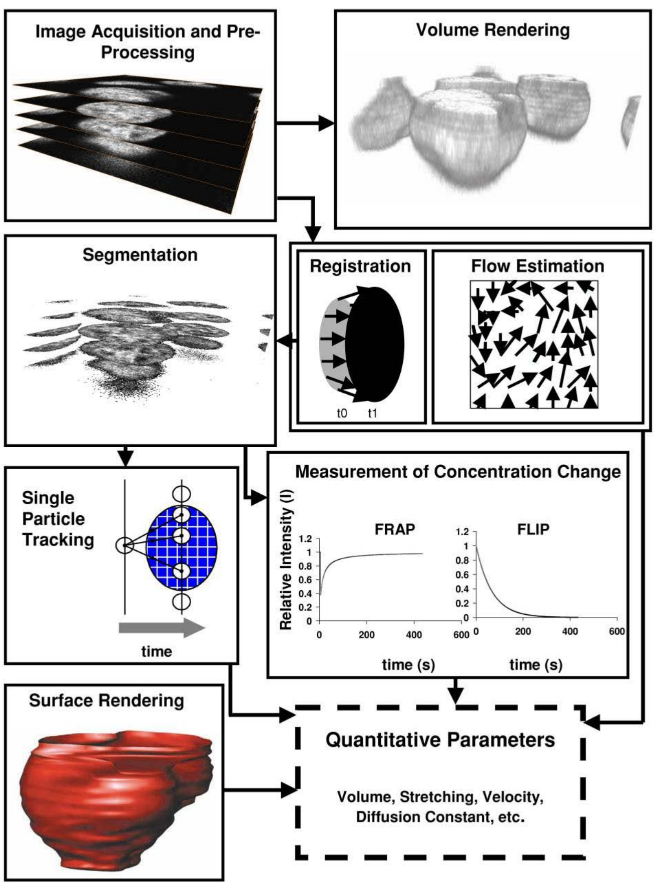

Figure 5: The typical workflow in computational imaging is presented.

[Eils and Athale 2003]

Figure 5 shows the typical computational imaging work-flow in cell biology. After the images of the sample have been acquired by microscopy. They have to be preprocessed to improve the signal-to-noise ratio. Then they can be directly visualized by methods like volume rendering. In the case of multiple objects in motion in which a particle is tracked over different time-steps the single particle tracking method is mostly used. This method gives access to various parameters, like velocity, acceleration and diffusion coefficients. To make a surface rending, it is needed to segment the contours of each individual section and give rise to volumetric measurements such as volume and surface area. At last, to make a measurement of concentration changes for the segmented areas in FRAP [2] or fluorescence loss in photobleaching experiments. [Eils and Athale 2003]

3.1 Light microscopy - electron microscopy

This chapter is about the basics of microscopy methods to study biological cells. Without the understanding of the structional organization of cells it is hard to learn about the cells function. First of all is the optical microscopy, it is the oldest and simplest but not irrelevant. In the last few years it even became more important, largely because of the development of methods for the specific labeling and imaging of individual cellular components and the reconstruction of their three-dimensional architecture. The most relevant advantage of the optical microscopy is probably that the light of it, is not destructive. So, with the help of fluorescent proteins the movement, dynamics and interactions of a living cell can be observed without harming it. The problem with optical microscopy is the limitation in resolution by the wavelength of visible light. This can be compensate with the use with a beam of electrons instead. Electron microscopy can image macro-molecular complexes within a cell at almost atomic resolution and even in three dimensions.

Even though optical and electron microscopy are important methods, but sometimes they are still not sufficient. Further methods will be mentioned in section 3.3 and 3.4

3.2 Obtaining samples

This section will present a technique to get sample data of cells, it is called the cryo-electron tomography. Figure 6 makes a schematic example of how such data get be obtained. After vitrification of the sample (a), either by plunge freezing or by high-pressure freezing, complex samples are navigated by correlative microscopy (b) and identified areas of interest can be further processed by vitreous sectioning (c) or focused ion beam micromachining (c*) for subsequent tomographic analysis in the electron microscope (d). [Plitzko et al. 2009]

How such samples look like, shows the figure 7[3] of the cryo-electron tomography of a "PRRS"-virus

3.3 Electron tomography

Electron tomography (ET) is a three-dimensional technique that makes biological structures suitable to study with nanometer resolution. This method allows the exploration of a large range of biological specimens (e.g. biologic cells). Wherever in an isolated state or in their cellular context. In the last decade the electron tomography had an exponential growth by some technological advances in methods and instrumentation. It has made a significant impact in understanding the cellular world. While the accomplished results of ET are already remarkable, it still remains a young technique with a lot of potential. Currently there is development towards large-scale automation, higher resolution, macromolecular

[2]FRAP (Fluorescence recovery after photobleaching) is a method in microbiology and biophysics to measure the diffusion speed in cells and thin liquid films

[3]PRRSV -https://goo.gl/PdpaBU

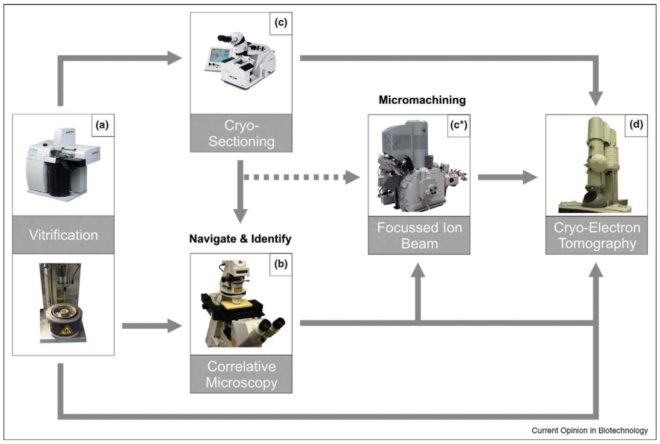

Figure 6: .
[Plitzko et al. 2009]

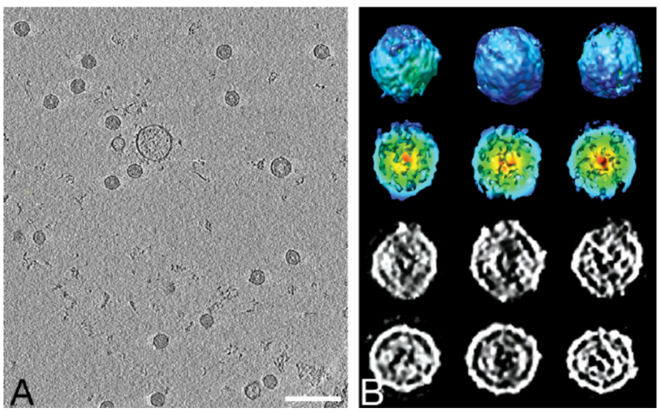

Figure 7: Cryo-electron tomography of PRRSV, (A) shows the virus and (B) shows the tomography plus the construction of a 3D model.

labeling and integration with other imaging techniques. Therefore ET hold promise to extend its role as a pivotal tool in structural and cell biology in the near future. Basically the output of ET can be considered as a 2D projection of the imaging specimen. The third dimension is retrieved using the same mathematical principles that underlie other 3D imaging techniques such as X-ray computerized tomography (CAT-scan) or positron emission tomography (PET). The common central idea is the collection of a series of 2D projection images from different orientations, which are later combined to yield a 3D reconstruction of the specimen. [Brcena and Koster 2009]

Figure 8 shows bright field (BF) and combined BF and fluorescence overview images of Hela cells grown on sapphire discs (A and B, respectively). The sapphire discs were clamped in the standard CLEM carriers and hence the bars of the finder grid are visible. The sample was high-pressure frozen and freeze substituted to Epon, and the cells were retraced for EM (C). One of the fluorescent structures was further studied using Electron Tomography (D). Shown is one slice of the tomogram and the model of an endosome (green). Two extensions can be observed extending from the endosome (arrows). Some other structures can be observed that are modeled in other colors that were potentially connected to one of

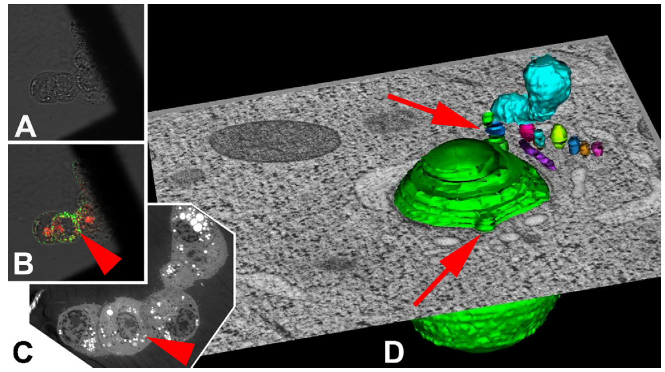

Figure 8: From an light microscope overview to high resolution Electron Tomography

the extensions. [Brown et al. 2009]

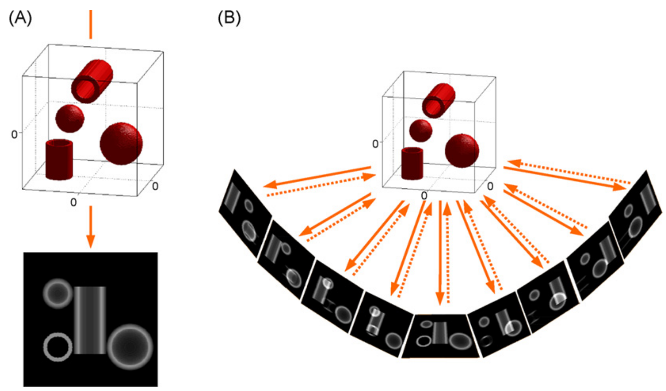

Figure 9: Electron tomography
[Brcena and Koster 2009]

"Figure **??** shows at (A) an individual image of a specimen, which is insufficient to unravel its 3D structure. For example, in the 0 projection image of this specimen, the small tubule and the small vesicle have similar profiles and it is not possible to ascertain whether the four individual objects are separated in the third dimension. These ambiguities can be resolved by collecting images of the specimen from different directions, which is the basic principle of ET. (B) During ET data collection, the specimen is projected at different tilt angles into a series of 2D images (continuous arrows). The back-projection algorithm essentially reverses this process in the computer. Each recorded image is smeared out along the projection direction (discontinuous arrows), and their added contribution yields a 3D representation of the specimen: the tomogram." [Brcena and Koster 2009]

3.4 Soft X-Ray Tomography and Correlated Cryo-Light Microscopy

Another method is the soft x-ray tomography combined with the cryo-light microscopy. It is important to get knowledge about the cellular architecture and the location of the specific molecules within this framework. To fulfill this task the two correlated cellular imaging techniques can be used. Cells are first imaged using cryogenic fluorescence microscopy to determine the location of molecules of interest that have been labeled with fluorescent tags. The same specimen is then imaged using soft X-ray tomography to generate a high-contrast, 3D reconstruction of the cells. Then the two data-sets are combined to produce a composite, information-rich view of the cell. This approach can be applied across the spectrum of problems encountered in cell biology. It can be used in other tasks than visualization of biological specimens, like basic research, biotechnological and biomedical applications such as the optimization of biofuels and the development of new pharmaceuticals. [McDermott et al. 2012]

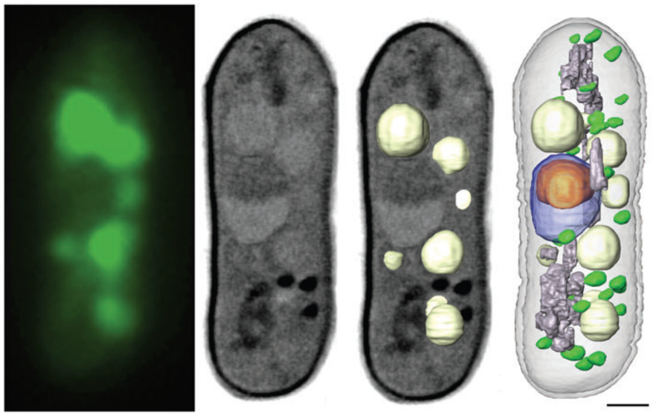

Figure 10: Correlated soft X-ray tomography and cryo-light imaging (wide-field fluorescence).
[McDermott et al. 2012]

”Figure 10: (a) The vacuoles fluorescently labeled and imaged by cryo-light microscopy. (b,c) Slices through the volumetric reconstruction calculated from soft X-ray tomography data, with the vacuoles shown as segmented volumes in panel c. The segmented vacuoles correlate closely with the locations determined from cryo-light microscopy. (d) The same cell after the major organelles have been segmented. The nucleus is shown in blue, the nucleoli in orange, mitochondria in gray, vacuoles in light gray, and lipid droplets in green. Scale bar = 1 m.” [McDermott et al. 2012]

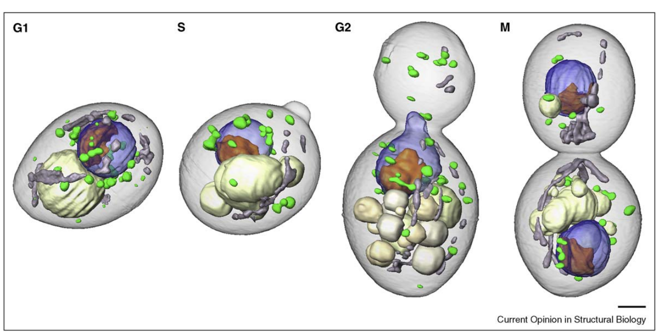

Figure 11: X-Ray 1
[Larabell and Nugent 2010]

Figures 11, 12 and 13 show some other example from Larabell et al. [Larabell and Nugent 2010]

”Figure 10 gives an illustrative example for correlating a cellular region from the scale of the light microscope to the high magnification and relatively small field of view of the electron microscope. The red arrows indicate areas enlarged in subsequent panels. (a)

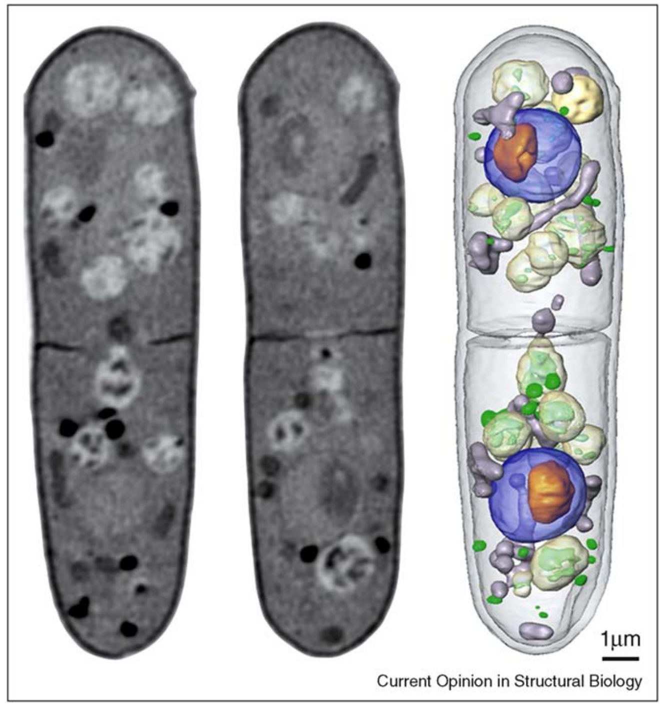

Figure 12: X-Ray 2
[Larabell and Nugent 2010]

Live cell, phase contrast image and (b) cryo-fluorescence image of neurons labeled with FM1-43 grown on EM Finder grids. (c) Corresponding cryo-EM image of the region exhibiting various neuronal processes surrounding the area where the tomogram was recorded. (d) Tomographic slice showing two neuronal processes, and an extracellular vesicle connected to one of the processes and to a protrusion from the other. (e) Surface rendering showing the extracellular vesicle (blue), two neighboring neuronal processes (gray), connections between them (yellow and orange) and some vesicle-bound molecular complexes (external: green; internal: red). The vesicle is shown in a cut-away view to expose the complexes.” [Plitzko et al. 2009]

4 Video Games

With the shift in the general perception of applications for PCs, new markets emerged over the past decades. Especially the entertainment business has taken a huge growth out of this emerging process. Nowadays the video gaming industry revenue amounts to over 101.62 billion dollars each year. [Statista 2016] This industry has grown that important that even the movie industry is trying to make a fortune out of this growth and more and more TV blockbuster films are made about TV games, their plot and their background stories. Since the rise of the first video games on the PC platform in the 1980s, the video game industry has changed dramatically. Whereas such games were considered as nerdy and only played by a certain percentage of the public back then, the acceptance for video games has flipped completely.

Nowadays video games not only accepted and played by the majority of the youth, they even managed to closed the gap from being a pastime to be considered as a type of artwork. The fasci-

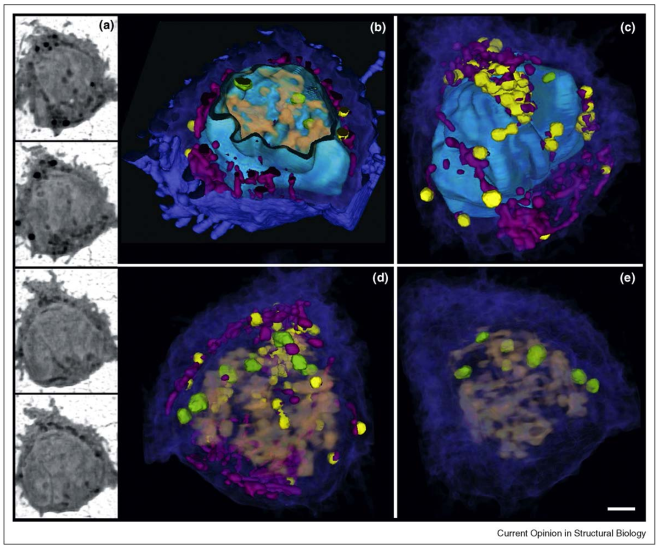

Figure 13: X-Ray 3
[Larabell and Nugent 2010]

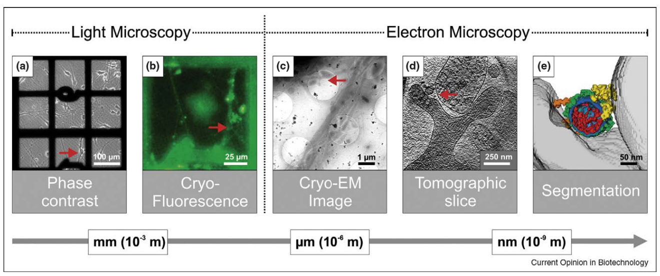

Figure 14: Correlative microscopy of mammalian cells.
[Plitzko et al. 2009]

nation about emerging in the digital deeps of imaginary worlds has led to the creation of cults about certain video games. Remarkably the fanbase of all kinds of video games is incredibly strong as its comprised by people of all ages. Especially communities of online games build up whole fantasy world where one can emerge fully into the plot. Such plots are comprised of various complex storylines that are entangled with each other and force the player to make various decisions. A very interesting aspect of those games are very steep learning curves in relation to the story and game mechanics. Many people that fully emerge into the illusion of such games show a deep understanding for the plot only shortly after starting to play these games. These observations lead to various deliberations whether such steep learning curves could be achieved in other game settings like educational games about physics, chemistry or biology.

5 Educational Games

Another emerging keyword within the game development of the last decade is "serious games". The idea behind these games is that the high motivational factor of video games could be used to support people in different serious situations like rehabilitation after an accident or a disease. Another field of application within the serious game industry are the so called "educational" or "instrumental" games that seek an increase the motivation of a learner within an educational process and therefore enhance the learning experience. The fact whether an game is educational or not is basically not clearly distinguishable since possibly any game could be used for an educational purpose - this is just matter of the selected purpose. Nevertheless educational games have a clear definition, According to M.D. Roblyer[Roblyer 2012]:

> *an instructional game is instructional software designed to encourage student motivation to include learning within a fun activity*

Another outcome of such concepts is called "gamification" and means that game specific elements like achievements or highscores are put in a completely different context to keep involved persons highly motivated. The concept of including games, or game specific elements like done in the gamification, into the education of kids and young adults is not new at all. Indeed there were already such concepts in the philanthropic education of the 18th century.[Overgoff 2004] Especially educational games for very young children are quite popular, in order to aid them learning basic maths, the alphabet or words. Such games can have various purposes and imply a variety of different tasks. Figure 15 shows such an educational game for little children that should support them in a playful way while learning the basic mathematics.[4]

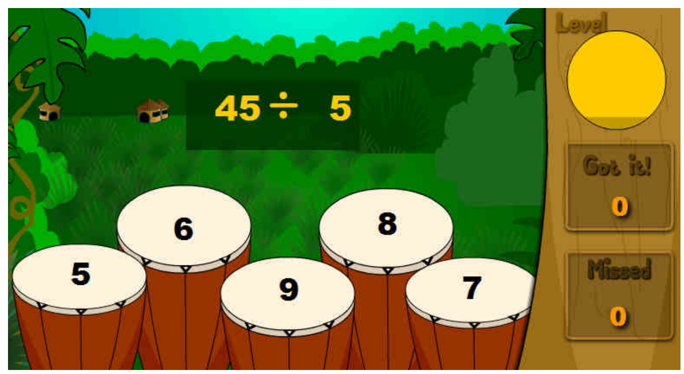

Figure 15: Educational Game Jungle Jim and the Donga Dinga Drums

Of course the concepts of the usual game design need to be adapted and evaluated for the purpose of integrating these games into the modern educational systems and standards. Nevertheless many experts have dealt with this topic in the last decades. Jayakanthan says about the use of computers in education [Jayakanthan 2002]:

> *Games as a whole are one of the most interesting ways for pupils to learn new things. The use of the computer in education is generally thought of as a panacea by itself. It must be understood that without proper methodologies, the computer cannot realize its potential as a tool for education. To fully utilize the power of digital technology in the classroom, we need to emphasize the development of a framework as such for the deployment of computers in the field of education. In particular, the computer gaming industry must realize the enormous opportunity which has opened up as a result of such initiatives being undertaken by educators.*

[4] http://www.multiplication.com/games/play/jungle-jim-plays-drums

Although the use of contemporary media such as film and the internet for educational purposes is largely accepted and optimized, current educational processes are mostly lacking support for the basic application of games for educational tasks. A counterexample to this premise has taken place in 2007 at the university of Stuttgart: Mnz et al. conducted an experiment concerning the application of such a game in the educational plan for a course at the university of Stuttgart. Essentially they used an educational game in one of their courses to empower the motivation and understanding of their students for linear time invariant systems in the time and frequency domain. In the courses of the semester the students have to design controllers for the submarine they have to maneuver in the game as shown in figure 16. The disadvantages of each of those controllers is shown through the struggles the students have to steer. At the end the students have a expert mode where they can utilize up to four controllers for 4 submarines to compare the different controllers to each other. Mnz et al. performed an evaluation of this educational game in February 2007 with more than 150 students. This evaluation showed that about two thirds of those student marked the question if the game had helped them to understand the course material with a ”totally agree”.[Mnz et al. 2007]

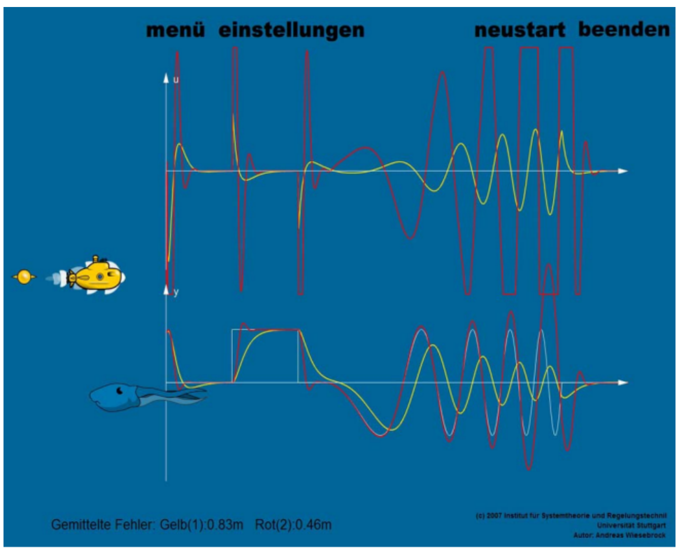

Figure 16: Submarine educational game: Input/Output signals after a single run with two submarines

5.1 Background Theories of Education Games

Different learning theories demand different views on the topic of educational games. To understand those views and to give raison d’łtre for educational games a variety of different theories regard the learning process shall be given. On behalf of clarity these theories will cover especially the following concepts:

- *Entertainment Education Concept:* Shows the basic concept why entertainment is useful in education
- *ARCS-Model:* Basic model for increasing and maintain motivation
- *Flow:* Method for understanding & implementing motivation; builds a bridge between motivational design theory and educational games
- *Game based learning cycle:* Cyclic model about the educational process within a game

These presented theories and concepts have and interconnection to each other and together build a theoretical educational thought basis on the topic of developing a educational game. [Song and Zhang 2008] shows with figure 17 the basic interconnection of those educational theories in respect to the design process of an educational game.

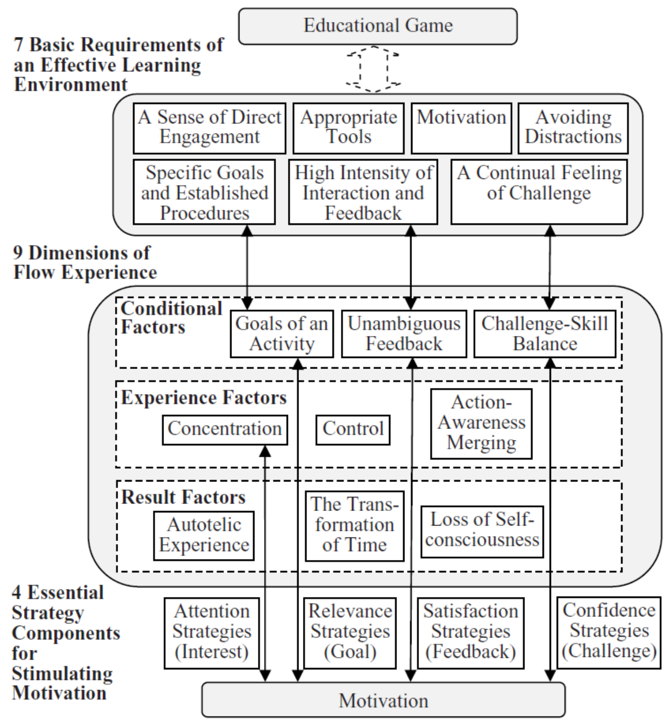

Figure 17: Interconnection of motivation, flow and learning environment theories in respect to educational game design

5.1.1 Entertainment Education Concept

[Hoblitz 2014] describes in her book the basics of educational – and generally serious – games the history of educational games and the interaction and view of different pedagogues on educational games. For example refers Hoblitz to the ”Entertainment Education and Video games” concept of Ritterfeld and Weber. This concept explains 3. possibilities how game and education contents can be combined:

1. *motivation paradigm:* This combination possibility applies entertainment elements as door opener in order to increase the players interest for a certain topic. A precondition for this combination is a not sufficient motivation within the educational topic

2. *reinforcement paradigm:* This combination possibility applies the entertainment elements as positive reinforcements like in-game cash, points or other awards. The current tag ”Gamification” relies heavily on this approach. Ritterfeld and Weber however criticized the fact that this approach can not be applied to complex learning goals.

3. *blending paradigm:* This combination possibility demands a parallel conductment of entertainment and education. The learning goal shall be achieved by incidental educate the user while playing.

5.1.2 ARCS Model of Motivational Design

The ARCS Model was created by Keller on the Florida State University and is based upon the idea of four key elements that are responsibly for encouraging the users motivation to learn during the learning process. As stated by [Song and Zhang 2008] motivation does not solely affect the length of the learning activity, but also enhances the efficiency and improves the effect. To gain a deeper understanding the ARCS Model shall be given[Keller 2016][Pappas 2016]:[Poulsen et al. 2008]:

1. *Attention:* Basically the attention part of the ARCS model represents the subjects attention. Keller suggested that this attention may be obtained by the following measures:

   - *perceptual arousal:* A learners attention should be gained by surprise, doubt or disagreement
   - *inquiry arousal:* A learners attention should be gained by challenges or problems that stimulates the learners curiosity
   - *variability:* A learners attention should be gained by an varied presentation of the topics

   Some methods of gaining the attention through these measures include the request for active participation to embedd the user into the learning process, for example through games or role plays. Goal is to entangle the subjects into the learning process through participation. Other methods are the application of humor throughout the learning process or the deliberate presentation of statements or facts that could cause a conflict with the believe of the learner.

2. *Relevance:* The relevance part of the ARCS model is responsible to build up a relation between the learning topic and the learner. A learner should reach a personal goal. Keller suggested that the relevance can be established by the following measures:

   - *goal orientation:* The educational process should meet the learners needs
   - *motive matching:* Provide appropriate influences to the learners
   - *familiarity:* Tie the instructions of the learning process to the learner experiences

   There are several strategies that were suggested by Keller to fulfill this part. One demands that the learner should link the new information presented to a previous experience he already gained. This gives the learner a sort of continuity and thus is a very good motivation strategy. Another strategy is that especially adult learner should be presented the skills they will gain while participating in the educational process. Giving the learners the possibility to choose their own instructional strategy is capable of affecting the learners motivation aswell in this context.

3. *Confidence:* The confidence part of the ARCS model is responsible to give the learners the feeling that they can succeed. A learner that does not believe that he can accomplish his goals looses motivation. Keller suggested that the confidence of the learner could be established by the following methods:

   - *learning requirements* Provide learning standards to establish positive expectations
   - *success opportunities* Present varied challenges in order to experience success
   - *personal control* Allow learners to attribute success to personal effort

   Keller suggests various ways to build up confidence in the learner, like to facilitate the self growth and encourage the learners to take own small steps and show them their progress. Other ways are to clearly communicate prerequisites and objectives to the learners. This will result in realizing that they can achieve goal in the educational process. Another possibility would be to provide feedback to the learners about their progress. Giving the learners some degree of control over their own learn progress – e.g. what lesson would be the next - is also highly motivating because the learner will have the impression of independence and control.

4. *Satisfaction:* The satisfaction part of the ARCS model is the 4th and last part and is primarily responsible to give the learners a reward for attending the educational process. . Keller suggested that the confidence of the learner could be rewarded by the following methods

   - *intrinsic reinforcement* Encourage intrinsic enjoyment
   - *extrinsic rewards* Provide rewards and motivational feedback
   - *equity* Maintain consequences and standards for success

   Keller suggests especially two strategies how this can be accomplished. One of them is the ”Praise or reward” strategy, where a learning process needs to present some kind of reward to the learner, this may be an accomplishment for example. The second one refers to the immediate application of the learned materials. This would give the learner the urgent feeling that his newly acquired skills will be useful in the future.

5.1.3 Flow

[Csikszentmihalyi and Csikszentmihalyi 1998] first described the phenomena of humans in a so called ”flow state”. Csikszentmihalyi describes flow on the official flow website [Centre 2016b] as followed:

> *Being completely involved in an activity for its own sake. The ego falls away. Time flies. Every action, movement, and thought follows inevitably from the previous one, like playing jazz. Your whole being is involved, and youre using your skills to the utmost.*

Basically the 9 Flow Dimensions is a theory that builds according to [Song and Zhang 2008] a bridge between educational design and motivational design theory. The theory has been confirmed in the use of network and has been applied in the man-machine interaction. The 9 Dimensions of Flow according to [Centre 2016a] are:

1. *Challenge-skills balance:* The balance between the challenge and the learners skills has to be within a certain range, exciting but not overwhelming – If the challenge is too hard the learner will get frustrated, while when its too easy he will get bored

2. *Action-awareness merging:* Within the flow process the learners thoughts won't drift towards something that has happened any when or might happen – The learner is only focused on the task.

3. *Clear Goals:* Within a flow experience the learner does not experience contradictory demands and has a clear idea of what should occupy his attention.

4. *Unambiguous Feedback:* During a flow experience a learner does not need to evaluate the last steps as he is aware of his performance all the time.

5. *Concentration on the task at hand:* While experiencing a flow, a learner is only aware of the task at hand – All unrelated things get ignored due to the concentration narrowing down the learners attention

6. *Sense of control:* During the flow experience an learner witnesses an absolute sense of personal control.

7. *Loss of self-consciousness:* Within a flow state a loss of self-consciousness appears – Opposite to non-flow experiences a lack of bodily needs appears.

8. *Transformation of time:* During a flow experience the learner experiences a distorted sense of time – Either it slows down or speeds up significantly.

9. *Autotelic experience:* As as Flow experience is an intrinsically rewarding activity it becomes automatically

[Song and Zhang 2008] mention that Nobak et al. classified Csikszentmihalyi's 9 dimensions into three categories:

- *Conditional factors:* Stimulate Flow experiences; include goals, feedback and challenge-skill balance
- *Experience factors:* Feeling of the subject within the flow experience like concentration and control
- *Result factors:* Results of the experience, like loss of self-consciousness, distortion of time etc.

5.1.4 Effective Learning Environment

According to [Song and Zhang 2008] the concept of a learning environment describes the integration of conditions which promote a learners development. This integration shows significance and possibility for the creation of a learning environment. Designing such an environment means to create a positive, motivating and effective learning platform in order to help a learner master the optics and material that accompany the educational goal. [Song and Zhang 2008]states the seven basic requirements of an effective learning environment according to Norman in his paper:

1. *High intensity of interaction and feedback*
2. *Specific goals and procedures*
3. *Motivate*
4. *Challenging setting; care about Challenge-skills balance*
5. *Direct Engagement; produce feeling of direct experiencing the environment*
6. *Appropriate tools; should fit learner and task, should not distract*
7. *Avoid distractions and disruptions*

5.1.5 Game based learning cycle

Additionally [Hoblitz 2014] discusses the game-based learning cycle of Garris, Ahlers and Driskell. This concept represents the basic serious game, and therefore also educational game, model. This approach is not state of the art anymore, but many of the most recent models derive from this. The basic idea of Garris, Ahlers and Driskell was to give the player autonomy through serious games. In their opinion such games have the potential to achieve this goal. The potential of these games is determined by through their storylines, challenges, riddle, goals and rules according to Garris, Ahlers and Driskell. Through the combination of instructional (educational) content and game characteristics a game cycle is triggered. Within this cycle the player issues one or more judgments about the game. Those judgments however influences heavily the user behavior and feelings, like joy, frustration, etc. The feelings on the other hand influence again the user behavior, which subsequently influences the system feedback. This continuous process is heavily interactive. During this continuous process the user evaluates the system feedback in relation to his own behavior. This process leads to a implicit comparison of the virtual world and the reality which can lead to experience and knowledge gain. Figure 18 illustrates this process.[Hoblitz 2014]

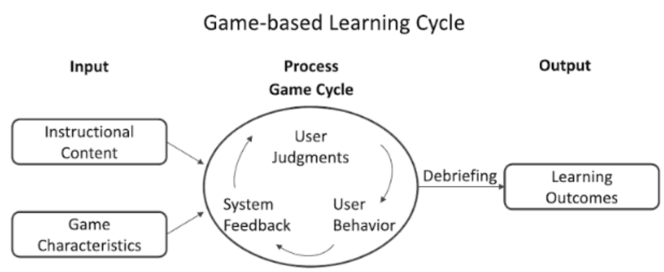

Figure 18: Game Model by Garris, Ahlers and Driskell

5.2 Difficulties of Educational Games

As mentioned the video game industry, although developing in an exceedingly fast process into different directions, is not capable of realizing the full potential of the computer as an tool for educational purposes without dealing with a set of different theories, requirements and quality indicators during game development.

5.2.1 Requirements characteristics

[Aslan and Balci 2015] described in their article certain characteristics of requirements an effective development process of a educational game has to fulfill:

1. *Requirements accuracy:* describes the representational correctness of a requirement. Can be divided into two subentities:
   (a) *Requirements verity:* sustains that the transformation from high abstraction levels to a specific dorm is done with enough accuracy to preserve the essential assertions.
   (b) *Requirements validity:* sustains that the requirements represent real needs of the learned in respect to the educational process.

2. *Requirements clarity:* describes how understandable and distinguishable the requirements are.

   (a) *Requirements unambiguity:* describes whether the statement can be interpreted in one or more ways.

   (b) *Requirements understandability:* describes the characteristic whether the requirement can be comprehended without any prerequisites by all readers

3. *Requirements completeness:* describes whether the requirements includes all necessary informations.

4. *Requirements consistency:* describes whether the requirement is distinguishable or in conflict with other requirements.

5. *Requirements feasibility:* describes how difficult the implementation of a single requirement is.

6. *Requirements modifiability:* describes how easily the requirement can be modified.

7. *Requirements stability:* describes the stability of requirements during a change of the game design within the development process.

8. *Requirements testability:* describes how easy the testing of a certain requirement can be performed.

9. *Requirements traceability:* describes how easy requirements that are related to the specific requirement can be found

5.2.2 Quality indicators

Additionally [Aslan and Balci 2015] identified in their article a number of different quality indicators for educational game development:

1. *Acceptability:* Describes the property of the game that determines wether the learning objectives and other system requirements are met for the game

2. *Challengeability:* Describes the property of the game that determines the level of exite-and inspirement a user feels while playing the game

3. *Clarity:* Describes the property of the game that determines wether the systems is easily understandable and unambiguous

4. *Effectiveness:* Describes the property of the game that determines how effectively the game can be integrated into the learn process of the subject. Especially seen in relation to other pedagogies - should be significantly better.

5. *Engageability:* Describes the property of the game that determines the degree of Addiction a user witnesses by playing the game.

6. *Enjoyability:* Describes the property of the game that determines the degree to which a user finds the process of playing the game fun.

7. *Interactively:* Describes the property of the game that determines how many interactions a user can perform actively while playing the game.

8. *Localizability:* Describes the property of the game that determines the adaptability of the game to satisfy needs of different languages (e.g. different charsets of text etc.), different cultural needs (symbols, actions) or different local standards like calendar, time zone, time and date representation etc..

9. *Rewardability:* Describes the property of the game that determines the degree to whiche the educational game introduces different types of rewards like achievements, medals, bonus points etc.

10. *Simplicity:* Describes the property of the game that determines how easily the game can be understood (What prerequisites needs the user to play the game)

11. *Transformativeness:* Describes the property of the game that determines how well the game transforms the subject learning in comparison with other pedagogies

12. *Usability:* Describes the property of the game that determines how easily the system can be set up for the intended use.

5.2.3 Learner Modelling

[Khenissi et al. 2015]reviewed in his article "Learner Modelling Using Educational Games: A Review of the Literature" different scientific approaches to create a holistic model of the learner. These models can later be used to elevate the learning potential of educational games by adapting the future games by utilizing the information gained from these models. According to his summary of different scientific publications a series of researchers tried to create a model of the learner by assessing a set of actions performed by the learner while playing the game. This model could be used to gain a better understanding of the learning process.

According to Khenissi, another critical part in modelling the learner, the motivational state of the learner, was assessed by Stathacopoulou et al.(2004). For achieving a greater understanding for motivation techniques they logged the all available information about the users actions together with a timestamp. After the logging process they defined action related to each type of evidence of the learners motivational state. This aspect of the learner model could be used to increase the excitement of the learners and therefore their enjoyment of the game.

Despite the obvious benefits like a wide spectrum of application, empowering the learning process through playful learning experiences, high motivational state of the user and adaptability to different need of the users common educational games have not been very successful in the past decades. One approach for explaining this circumstance was presented by [Myers 2014] in his article:

> *[A]ccording to Crawford, the best measure of the success of a game is that the player learns the principles behind that game while discovering inevitable flaws in its design . A game should lift the player up to higher levels of understanding.*

According to this statement, the lack of lack of a challenging game design inevitable leads to defeat of the purpose of such a educational game.

5.3 Examples of Educational Games

Nevertheless there are many current used educational games that support various educational topics. In this section a few real educational games within the topic of visualization of cell processes are presented.

5.3.1 Cellcraft

Cellcraft is a non commercial basic educational flash browser game where the player controls a cell. This game lets the player explore all the different organelles and their features of their cell and provides a nice game design that allows the player to understand the basic processes of within a cell. The following statement of the developers explain the setting of cellcraft[Team 2010]:

> *Exploring the cell through gaming. Build a cell, fight off viruses, survive harsh worlds, and save the Platypus species! This game was made possible by a grant from the Digital Media & Learning Competition. The goal was to make a truly educational game that was also genuinely fun to play. We hope students, teachers, and gamers will all enjoy the game. Our forums now have open registration as well! There has been some debate as to the games views on evolution and creation. Please read our response and weigh in with your thoughts and opinions on the subject. Thanks!*

The game is separated in several levels where the player has to ”equip” his cell with new organelles and features in order to adapt to the new environment. During the course of the game the player is confronted with a range of different dangers like running out of ATP, viruses and bacteria. Figure 19[5] aswell as figure 20[6] show pictures of the ingame footage of Cellcraft.

Figure 19: Ingame Footage Cellcraft

5.3.2 Spore

Spore is basically a commercial game that deals with the evolution of life as we know it. At the beginning the player starts with some microbiological cell that he need to evolve in order to survive. In the course of the game evolutional processes are explained to the player which maker this game somewhat semi-educational[Inc. 2008]. The developer describes spore as followed[7]:

Figure 20: Ingame Footage Cellcraft

> *From Single Cell to Galactic God, evolve your creature in a universe of your own creations. Play through Spore’s five evolutionary stages: Cell, Creature, Tribe, Civilization, and Space. Each stage has its own unique style, challenges, and goals. You can play how you choose start in Cell and nurture one species from humble tidepool organism to intergalactic traveler, or jump straight in and build tribes or civilizations on new planets. What you do with your universe is up to you. Spore gives you a variety of powerful yet easy-to-use creation tools so you can create every aspect of your universe: creatures, vehicles, buildings, and even starships. While Spore is a single-player game, your creations are automatically shared with other players providing a limitless number of worlds to explore and play.*

Figure 21 shows a picture of the ingame footage of the microbiological cell phase in Spore[8].

5.3.3 Thrive

Another educational game that deals with the topic of cell evolution is thrive, a free, open source game. Basically thrive resembles spore in certain things. The project is fully open source and non commercial and everyone can contribute. The developers describe thrive as stated[Studio 2016]:

> *Thrive is a free, open-source game currently being developed by an online volunteer team called Revolutionary Games. Drawing inspiration from numerous simulation and strategy games (in particular the original concept behind the PC game Spore), Thrive is a game about a species evolution from unicellular organisms to galaxy-wide space travel. Our team seeks to accomplish two major goals: create engaging, compelling gameplay that respects our players’ intelligence,and remain as accurate as possible in our depiction of known scientific theory without compromising the former. The eventual game will contain powerful creation tools, allowing*

[5] http://files.fortressofdoors.com/images/cellcraft.png

[6] https://s-media-cache-ak0.pinimg.com/originals/ce/23/60/ce23607748f836ac2bfeadd87e5ede4dak.jpg

[7] http://store.steampowered.com/app/17390/

[8] http://tokyomi.com/wp-content/uploads/2008/09/spore_screenshot1.jpg

Figure 21: Ingame Footage of the cell stage in Spore

> *players to realistically craft organisms, technology, cultures, and even entire planets.*

Figure 22 shows a picture of the ingame footage of the microbiological phase in Thrive[9].

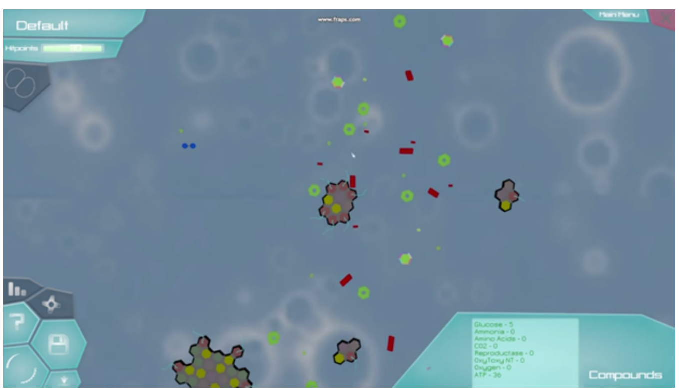

Figure 22: Ingame Footage of the cell stage in Thrive

6 Conclusion

As stated serious games – and in particular educational games – are an emerging application field for computer visualization. Though neither the idea of applying playful methods into an educational process, nor the idea of educational video games are new, the last decade indicates major improvements. Many theories and concepts nowadays deal with motivational factors and the integration of those into an educational process. Additionally many new design principles for educational games build up a basis for game design within this market. Though there are still plenty of difficulties to keep in mind and overcome, the modelling of the learner and various quality assurance approaches enhance the game design of educational games increasingly. As shown there are already a few educational games dealing with the visualization of cell processes, but the market is definitely expandable. To provide the learner with a meaningful game, a proper analysation of the biologic background is needed. To gather this information the described techniques of the electron tomography and the soft x-ray tomography with the correlating cryo-light microscopy gives evidence to be useful.The next part, probably a not easy one, is to prepare the gathered information and abstract it in a kind of way, in which no relevant information gets lost but also remains easy enough to use it effectively in a educational game. This would be interesting to see in a future "cell-game".

[9] `https://www.mediafire.com/convkey/1810/5u82knui8tln3nd6g.jpg?size_id=5`

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