SIMULATION DE SYSTÈMES CHIMIQUE ET PHYSIOLOGIQUE

par

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Sommaire

Ce mémoire est composé de deux parties, chacune correspondant à un article publié. La première présente une nouvelle approche de simulation pour une chimie virtuelle utilisée dans le domaine de la vie artificielle. Cette approche innovante est basée sur les échanges d'énergies lors des collisions entre les différents atomes du système. Les échanges d'énergie permettent de mieux diriger les réactions, tout en laissant une grande liberté au système. Cette chimie est développée dans l'optique d'étudier l'émergence de certains phénomènes chimiques en lien avec l'origine de la vie. La deuxième partie du mémoire traite d'une simulation d'un corps humain. Le système développé simule certains métabolismes importants du corps humain dans le but d'obtenir un humain virtuel pouvant être utilisé dans le cadre de la formation en sciences de la santé. Le système cardiovasculaire ainsi que le système respiratoire du patient virtuel ont été développés et sont présentés dans ce mémoire.

Mots-clés: Vie artficielle ; Chimie artificielle ; Approche ascendante ; Simulation ; Métabolisme virtuel, Simulation biologique, Modèle cardiovasculaire, Modèle respiratoire.

Sommaire

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Introduction

La simulation informatique permet de reproduire plusieurs types de phénomènes. Les simulations de phénomènes physiques et chimiques sont de plus en plus utilisées en recherche. Que ce soit la dynamique des fluides, les effets des forces gravitationnelles entre des étoiles et des planètes, ou encore les réactions chimiques entre différents atomes, toutes ces simulations tentent de reproduire à l'aide d'un ordinateur des expériences autrement plus complexes, voire presque impossibles, à reproduire dans un laboratoire. Un domaine de recherche particulièrement indiqué pour l'utilisation des simulations est la vie artificielle.

La vie artificielle est le domaine d'étude des systèmes liés à la vie, leurs processus et leur évolution, en utilisant des simulations informatiques, la robotique ou la biochimie. Dans ce domaine, l'une des questions fondamentales à laquelle la communauté cherche à répondre concerne la transition entre le non-vivant et le vivant *in silico* [3]. Cette transition pourrait s'effectuer de plusieurs manières différentes. Certaines simulations basées sur des chimies artificielles utilisent la correspondance de chaines de caractères [37]. D'autres encore utilisent des chimies artificielles plus réalistes représentant des atomes et formant des liens lors de collisions [21]. Ces différentes méthodes, même si elles peuvent représenter plusieurs phénomènes intéressants propres aux organismes vivants, ne permettent toujours pas d'explorer les mécanismes nécessaires à la transition entre le non-vivant et le vivant. C'est dans cette optique qu'une partie des travaux présentés dans ce mémoire a été développé. La solution proposée repose aussi sur une chimie artificielle. Cependant, contrairement aux autres chimies artificielles actuellement développées et utilisées, les réactions entre les différents atomes du système reposent sur des échanges d'énergie et respectent les lois physiques et chimiques de base. Cette nouvelle chimie virtuelle permet d'observer

l'émergence de phénomènes plus complexes qui peuvent nous aider à comprendre et à valider les mécanismes chimiques et physiques permettant l'apparition d'organismes vivants.

La simulation est aussi très utilisée pour la formation de la main-d'oeuvre dans plusieurs domaines. En sciences infirmières par exemple, la simulation permet de mieux préparer les futures praticiennes à des situations qui arrivent rarement. Cependant, la plupart de techniques actuelles consistent à utiliser des mannequins mécaniques ou des acteurs [15]. Ces solutions sont difficiles à mettre en place et présentent dans la plupart des cas un coût élevé. Une alternative est donc l'utilisation de simulations informatiques. Incorporé à un jeu sérieux (*serious game*), un simulateur pourrait reproduire certaines situations rares de patients admis à l'urgence. Le jeu serait lié à un tuteur virtuel, par exemple la plate-forme ASTUS (Apprentissage par Système Tutoriel de l'Université de Sherbrooke) développée au département d'informatique de l'Université de Sherbrooke, dans le but de donner une rétroaction adéquate afin que l'apprenant s'améliore et ce, à faible coût. Cette même plateforme s'occuperait de la définition des scénarios. Le simulateur n'aurait qu'à recevoir les conditions initiales du patient. Certains simulateurs existent déjà [16, 27] afin de reproduire le fonctionnement d'un corps humain ou d'une de ses parties. Cependant, le simulateur présenté dans la deuxième partie de ce mémoire utilise une approche différente afin de modéliser ces systèmes. Le simulateur définit seulement les interactions et les comportements de base des organes et des systèmes du corps et laisse les comportements plus complexes émerger seuls. Cette approche a le mérite d'être plus simple à implanter que les approches traditionnelles qui modélisent l'entité complexe directement. Le simulateur est donc plus apte à être utilisé pour la formation en sciences infirmières.

Ces deux projets peuvent sembler à première vue assez différents. Cependant, le développement de ces simulateurs s'appui sur la même idée de départ. Cette idée, c'est qu'en utilisant des concepts très simples et très bien connus, nous sommes capables de voir apparaitre des comportements beaucoup plus complexes, seulement en laissant ces concepts simples interagir ensemble. C'est ce qui se passe pour la chimie artificielle, où à partir d'interactions simples entre des atomes, nous pouvons observer des phénomènes chimiques plus complexes. Pour les systèmes cardiovasculaire et respiratoire du patient virtuel, l'utilisation de concepts simples nous permet de reproduire

les fonctionnements plus complexes des nombreux systèmes en interactions.

Ce mémoire comporte deux chapitres. Le chapitre 1 explique la chimie artificielle qui a été développée et présente les résultats de validation du modèle. Le chapitre 2 donne la description des différents systèmes développés pour le patient virtuel en plus des résultats.

Chapitre 1

Simulateur de chimie artificielle basé sur l'énergie

Résumé

Cet article présente une nouvelle chimie artificielle utilisant l'énergie comme contrainte sur les réactions lors des collisions entre les différents atomes du système. Ce simulateur de chimie artificielle permet d'observer l'émergence de certaines propriétés des systèmes chimiques telles que les distributions de Boltzmann pour les vitesses des molécules ainsi que le principe de Le Châtelier sur l'équilibre des réactions dans un système chimique. Ces différentes lois chimiques ne sont pas codées par le système, mais ont émergé des interactions de base des atomes. Cette nouvelle chimie artificielle représente les premiers pas d'une tentative plus large permettant de répondre à un problème important en vie artificielle. Ce problème est la transition in silico (à l'aide de simulations informatiques) d'un état non vivant à vivant. Les différents résultats obtenus démontrent que la nouvelle chimie réagit de façon cohérente et en respect des différentes lois chimiques. Le système atteint un équilibre chimique, mais continue tout de même de créer de nouvelles molécules. La chimie est donc constructive, c'est-à-dire qu'elle permet de construire une infinité de molécules différentes.

Commentaires

Cet article représente une partie de mon travail de maîtrise, durant laquelle j'ai développé un simulateur de chimie artificielle. Principalement en collaboration avec le professeur Claude Legault, j'ai développé le modèle chimique qui est présenté dans cet article dont je suis le principal auteur. J'ai obtenu les différents résultats au terme de diverses expériences avec le simulateur. L'article a été soumis et accepté à la 13^e conférence sur la vie artificielle (Artificial Life 13) qui a eu lieu à la Michigan State University à East Lansing au Michigan en juillet 2012.

Précisions sur le simulateur

Les quantités d'énergie requises pour briser un lien entre deux atomes lors d'une collision sont définies dans l'annexe A. De plus, il n'y a aucune limite fixe à la quantité d'énergie interne qu'un atome peut contenir. Cette quantité ne pourra toutefois pas dépasser la quantité totale d'énergie du système afin de respecter la loi de conservation d'énergie.

La grille mentionnée dans l'article est utilisée seulement afin de faciliter la simulation. La grille permet d'accélérer la détection des collisions entre les différents atomes. Comme les atomes ont une position fixe lors d'une tranche de temps, ils sont répartis dans chacune des cases de la grille qui représente l'espace de simulation en deux dimensions. Par la suite, le simulateur vérifie s'il y a des collisions entre les atomes présents dans chacune des cases. Sans cette façon de procéder, le simulateur devrait faire n^2 vérifications, pour n représentant le nombre d'atomes du système, ce qui limite la quantité d'atomes pouvant être simulés tout en gardant une vitesse d'exécution rapide.

Energy-based Artificial Chemistry Simulator

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Abstract

We present a new artificial chemistry simulator based on simple physical and chemical rules. The simulator relies on a simplification of bonding and internal energy concepts found in chemistry to model simple, large scale, chemical reactions without delay between computation and visualization. Energy introduction and removal can be controlled in the simulations in order to modulate reaction rates. The simulations demonstrate that with this simplified model of artificial chemistry coupled with the concept of energy, it is possible to see the emergence of specific types of compounds, similar to real molecules.

1.1 Introduction

The origin of life and the transition from non-living state to living state are fundamental questions that humans have pondered for many centuries. The auto-assembly and self-organization of molecular structures, in particular in biochemistry, are a continuing source of questions and study. The field of artificial chemistry aims to answer these questions. Of course, there are still many longstanding challenges in artificial chemistry. One of them is to demonstrate a model in which the transition to life occurs in silico [3]. The simulator presented in this paper aims at taking a novel route to achieve this goal.

The field of artificial life revolves around simulations to explain phenomena related to the origin of life like emergence, evolution, self-replication and adaptation. Some researchers [4, 24, 35] have developed techniques to create creatures that evolve and cooperate. Using genetic algorithms and neural networks, they created virtual organisms that reproduce intelligent behaviors and execute various tasks. Other researchers are interested in the phenomenon of self-replication [18, 36, 21]. Using artificial chemistry, these researchers were able to simulate simplified cells that reproduce themselves [21]. They were also able to reproduce biochemical pathways like the fatty acids oxidation [37]. Other researchers went further and made evolving biochemical pathways [31, 17].

One of the key properties of all living organisms is their ability to reproduce. Researches show that it is possible to obtain simple auto replicative molecules or organisms from artificial chemistry [36, 18, 19, 20]. [9] gives a definition of such artificial chemistry that is a triple $< S, R, A >$ where S is the set of particles, R is the set of reactions and A is the algorithm that applies the reactions. Using this definition of an artificial chemistry, it was demonstrated that rules can be specified that allow the replication of some molecules and simple cells [18, 21]. However, as explained in the third experiment of [21], it is necessary to randomly modify the state of the atoms to eventually obtain a cell that could use the defined set of chemical rules to replicate. The property of replication is explicitly defined within the different reactions, thereby limiting the possibility of evolution for the molecules. Emergence is hard to achieve, even if the rules are generic and mutations possible. In order to

find the right rules to achieve replication in his chemistry, Hutton created a simulator in the form of a game [22]. The artificial chemistry used in this simulator is based on the same principles used in his previous works. The possible reactions are defined by the user in each level to achieve a specific goal. Even if this method works well to resolve specifics problems, the fundamental concept of energy found in physics and chemistry is missing.

However, the simulation of actual chemistry and physics is computationally taxing. Numerous theoretical models exist to describe molecular structures and properties. For example, force fields exist to rapidly describe structural and conformational properties of molecules. These methods can be used on fairly large (i.e. biochemical) systems and molecular dynamics calculations [39]. They cannot however describe the electronic properties of the molecules, and reactions cannot be readily modeled. On the other hand, numerous quantum chemistry software packages exist to model electronic properties of molecules with varying degrees of precision [34]. They are computer intensive, and usually used to obtain single molecule properties. It is clear that formal computational chemistry software cannot be used to rapidly model and study dynamic reactions and emergent phenomena.

Simulating simplified concepts of molecular dynamics and reaction processes of organic chemistry and living organisms is actually more interesting for real-time applications. There are simulators that use this approach. Some of them are based on computer code [32, 33, 1]. Computer code forms programs in the core. When executed, these pieces of code can erase parts of other programs, changing them, thus developing different functional properties. The initial parameters of these simulations allow experiments on different conceptual environments like desert and jungle (more or less resources) and on different type of organisms. Even if these organisms have no equivalent in reality, their behaviors and their properties on the other hand, do. Our goal is to devise a new artificial chemistry simulator that will result in the emergence of dynamic chemical behaviors, through the use of very simple models.

A key concept of our system is to use simple forms of energy to define the chemistry. In [12, 13], the energy is used in relation to entropy to determine if an organism can replicate after processing a chain of bits. In our simulator however, a reaction between two atoms will occur if enough energy is involved during the collision. The

energy drives and controls the reactions and the evolution of the system. Explicit consideration of energy is in contrast to most rule-based simulators, where reactions occur when two atoms have the right type and a rule to link them.

The next section of this article will give a description of the simulator with the different components and the chemical and physical rules of the system. Results that demonstrate the functionality and viability of the system will be presented in the third section following by a discussion on further development of the simulator.

1.2 System description

The system developed can simply and quickly simulate dynamically a large quantity of various atoms. To achieve this, the system is based on an artificial chemistry to simplify calculations. The atoms collide with each other, based on the simple principles of kinematics. They can bind together or break the bonds between themselves by releasing or absorbing energy. The artificial chemistry is simulated onto a two-dimensional grid divided in rows and columns. The borders of the grid can exchange energy with atoms and molecules that collide with it to represent heating and cooling processes. An editor was developed to change the shape of the grid. It allows the specifications of properties for the borders of the container, such as their capability to release or absorb kinetic energy.

1.2.1 Components

The fundamental units of the system are the atoms. They are the components that allow all the interactions and the evolution of the chemistry. As with real atoms, our model atoms possess intrinsic properties: *type* (or element), *mass*, *radius*, and *valences*. The *types* are named after existing atoms $\in$ {Hydrogen, Carbon, Nitrogen and Oxygen}; the *mass* and *radius* are also defined to correspond to the actual atomic values. Finally the number of *valences*, which is the number of possible bonds that an atom can do with other atoms, is also defined from known atomic properties. In addition to these immutable properties, the atoms possess *energy*. The energy of the atoms varies throughout the simulation, but remains constant for the entire simulated

system in accordance with the principle of conservation of energy. In other words, energy variation on the atoms only occurs through exchange during collisions and chemical reactions.

Group of bonded atoms are called molecules. In the system, a molecule is not a defined entity, it is simply the result of atoms bonded together. Each atom contains its bonding information with other atoms. Molecules do not have any intrinsic properties, besides mass and molecular energy (sum of atomic masses and energies, respectively). These properties are calculated and taken into consideration in the event of collisions. However, since collisions always occur between atoms, either part or not of molecules, the term particle will be used throughout the paper to avoid ambiguities.

The energy of an atom is divided into three categories. *Kinetic energy* represents the energy associated with the motion of an atom in the simulation. It is directly related to its velocity. *Internal energy* represents a crude simplification of the internal vibrational and rotational energies of an atom. In conjunction with the kinetic energy, they are the available energy that an atom can transfer during a collision to break bonds. The last type of energy is the *bond energy.* It represents the electronic potential of an atom. It is the abstraction used to represent the energy stored in electrons to form bonds.

1.2.2 Chemistry and physics

Since we wanted a simulation without delay between calculation and visualization for a large number of atoms, a simplified physics was implemented. Two basic concepts of classical physics are used in the simulation, which are the energy and the momentum conservation.

When simulations start, atoms are positioned randomly onto the grid. To ensure motion in the simulation, they are assigned random velocities. This initialization influences the different collisions scenarios that happen throughout the simulation.

A collision between two atoms will occur only if these atoms are not already bonded together and their centers are at a distance less or equal to the sum of their defined radii, that represents their zones of interaction. Since bonding only occurs if the two atoms are not already bonded, there are some restrictions on the possible

shape a molecule can take. These restrictions will be discussed later.

Energy is a key concept in our simulation. Each atom possesses different kinds of energy. Bond energy represents a simplification of the behavior of electrons involved in chemistry. Bond formation involves pairing of two electrons located on two different atoms. When these two electrons pair to form a bond, they get stabilized, and thus release energy. This energy is transformed into internal energy. Each bond possesses a specific strength that can be defined as *dissociation energy*. It represents the energy required to break that bond and it corresponds exactly to the amount of energy released and transformed into internal energy during bond formation. All the dissociation energies are taken from empirical chemistry tables [7]. The energy available during a collision thus needs to be sufficient in order to break a bond. The way the atoms collide changes the energy available for a reaction to occur, which is different from a rule-based artificial chemistry.

Using this simple concept, there are four possible scenarios that can occur during inter atomic collisions. Independently of the scenario, there is always a transfer of internal energy between the colliding particles. This transfer is calculated with

$$E_{transfer} = \frac{(E_1 - E_2)}{2} F_{transfer} \tag{1.1}$$

where E_1 and E_2 are, respectively, the internal energy of the first and second colliding particles and $F_{transfer}$ is a constant transfer factor. This transfer factor represents the ratio of internal energy between the particles. A factor of one means the energy is distributed equally. It is the default value used by the simulator. The internal energy of each particle is then distributed with

$$E'_1 = E_1 - E_{transfer} \tag{1.2}$$

$$E'_2 = E_2 + E_{transfer} \tag{1.3}$$

where E'_1 and E'_2 are the new internal energies of each particles following the collision.

An atom with at least one free valence, called a radical, is a highly reactive atom. The first scenario occurs when each of the atoms involved are radicals. When they collide, a bond is automatically formed. There is a release of bond energy representing

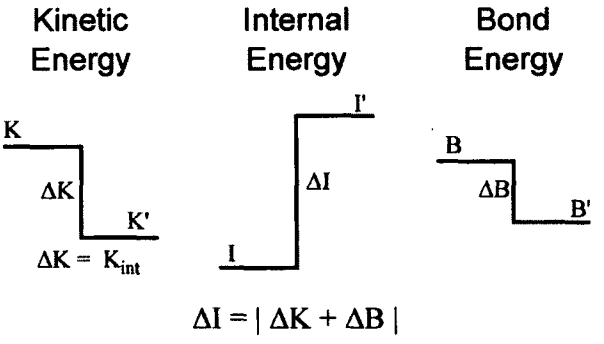

Figure 1.1: Energies transfers on bond formation. The energies are represented for the whole system in collision. The kinetic and bond energies decrease and are transformed into internal energy.

the bond formation and the electronic stabilization of the atoms. All this released energy is converted into internal energy and distributed to each atoms of the newly formed molecule as a function of their masses and the total mass of that molecule (Fig. 1.1). Since a bond is formed between the atoms, the resulting velocity of the newly formed molecule must be the velocity of the center of mass of the two particles colliding. This fact is explained by Koenig's theorem, which states that the total kinetic energy K_{tot} of a system is the sum of the kinetic energy of the center of mass with the kinetic energy of that system relative to its center of mass, termed *internal kinetic energy* (K_{int}). Since there are only two particles in the collision, the sum can be extended to

$$K_{int} = \frac{1}{2}m_1\vec{U}_1^2 + \frac{1}{2}m_2\vec{U}_2^2 \tag{1.4}$$

$$K_{tot} = \frac{1}{2}m_{tot}\vec{V}_{cm}^2 + K_{int} \tag{1.5}$$

where m_1 and m_2 are the masses of the first and second particle in collision, $\vec{U}$ are their velocities relative to the center of mass and $\vec{V}_{cm}$ is the velocity of the center of mass. This first scenario is therefore a perfectly inelastic collision. All the *internal kinetic energy* K_{int} is transformed into another form of energy, thus all the resulting kinetic energy is included completely into the velocity of the center of mass. The

velocity of the center of mass can be found with

$$\vec{V}_{cm} = \frac{m_1\vec{V}_1 + m_2\vec{V}_2}{m_1 + m_2} \tag{1.6}$$

where m are the masses of each initial particle and $\vec{V}$ their velocities. The *internal kinetic energy* K_{int} is transformed into internal energy. To summarize, when a bond is formed, there is a loss of kinetic energy corresponding to the *internal kinetic energy* of the Koenig's theorem and a release of bond energy representing the stabilization of the atoms. These energies are transformed into internal energy (Fig. 1.1).

For all three other scenarios, the available energy must be taken into consideration. The available energy is the *internal kinetic energy* (K_{int}) of Koenig's theorem (Eq. 1.4) for the two particles in collision. To this energy, a part of internal energy of the system in collision is added. This portion is taken in the same proportion as the *internal kinetic energy* (K_{int}) from Koenig's theorem. The energy $E_{reaction}$ required to break a bond is

$$\Delta E = F_{diss}E_{diss} \tag{1.7}$$

$$E_{reaction} = E_{diss} + \Delta E \tag{1.8}$$

where E_{diss} represents the *dissociation energy* of the bond and F_{diss} is a constant factor. In the simulator, this factor is set to 10%. This excess energy is used to transfer enough kinetic energy to the two atoms between which a bond is broken allowing them to move away from each other. When more than one bond can be broken, the one with the highest *dissociation energy* is chosen.

An atom without free valence cannot form any bond. When two atoms in that state collide, they can either bounce off each other or break one of their bonds. These are the second and third collision scenarios and are highly related. If the particles do not have enough energy available to break a bond, then the collision is modeled as a perfectly elastic one. The particles just bounce and there is no gain or loss of kinetic energy for the system in collision. Kinetic energy is however distributed normally by the principles of kinematics. The second scenario ends here.

Otherwise, if the colliding particles have enough energy to break a bond, the third

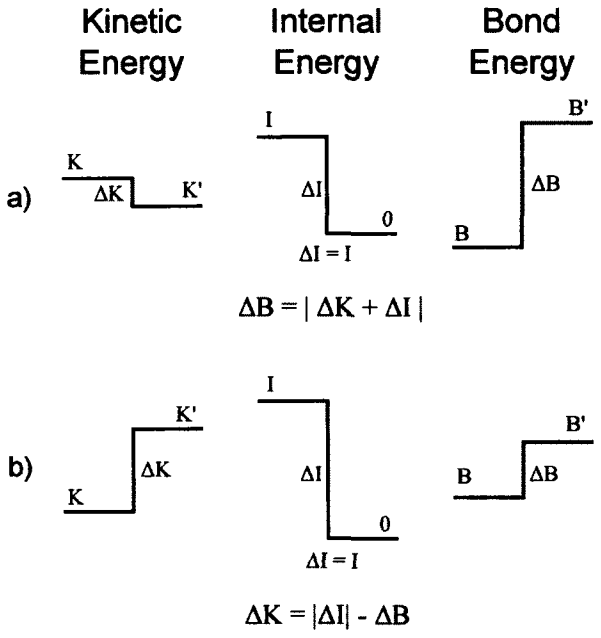

Figure 1.2: Energies transfers on bond dissociation. The energies are represented for the whole system in collision. There are two possible cases. Case a) occurs when the bond dissociation energy is larger than the internal energy. The remaining energy needed comes from kinetic energy. Case b) occurs when the bond dissociation energy is smaller than the internal energy. The excess is transformed into kinetic energy.

scenario occurs. This process can be decomposed in two steps, the first one being a partially inelastic collision. Since the required energy to break a bond can exceed the available internal energy of the system in collision, part of the *internal kinetic energies* of the particles is used to fill the potential well of the bond. As a result, the particles will move away more slowly than before the collision. This is the case a) of Fig. 1.2. On the other hand, if the required energy to break the bond is less than the amount of internal energy available, the excess of available internal energy is transformed into kinetic energy, resulting in the two particles in collision moving away faster than before the collision (Case b) of Fig. 1.2). The second step of this scenario is the scission of the bond. Again, the Koenig's theorem is used which also states that the sum of the momentum of each particle relative to the center of mass must be null. Thus, the extra energy ΔE used to break the bond will only be transformed into *internal kinetic energy* for the particles of the scission. The speed of one of the particles relative to the center of mass can then be calculated with

$$\|\vec{U}_1\| = \sqrt{\frac{2m_2\Delta E}{m_1(m_1+m_2)}} \tag{1.9}$$

where $\vec{U}_1$ is the velocity relative to the center of mass and m_1 and m_2 are the masses of the first and second particles. Since the calculation gives only the magnitude of the velocity, an exit angle relative to the center of mass must be set. This angle is arbitrarily set to 30 degrees in the simulation. The final velocity relative to the center of mass can be found with simple trigonometry from the exit angle and the magnitude of the velocity. To find the final velocity $\vec{V}_1$ of the particle back in the simulation frame (instead of the center of mass frame), the result of the elastic collision previously calculated (the bounce between the particles before breaking the bond) that represents the velocity of the center of mass of the molecule that is cleaved must be added to the internal velocity of the particle. Since the momentum must be conserved, $\vec{V}_2$ can easily be found with

$$\vec{V}_2 = \frac{(m_1+m_2)\vec{V}_{cm} - m_1\vec{V}_1}{m_2} \tag{1.10}$$

It is possible for a radical to collide with a stabilized atom. This corresponds to

the fourth scenario of collision. When this scenario happens, the simulator breaks a bond from the stabilized atom (scenario 3), freeing a valence. This case can occur only if there is enough energy in the system in collision to break that specific bond (Eq. 1.8). The newly formed radical is then bonded with the initial radical (scenario 1), stabilizing both atoms again. The atom previously bonded becomes the new radical since it has a free valence. The result is an exchange of atoms between the two molecules. This mechanism keeps the amount of radicals to a reasonable level. Fig. 1.1 and Fig. 1.2 summarize the change in energy for the dissociation and the bonding of two particles.

1.2.3 Molecular Geometry

The way the atoms are positioned around each other will have an influence on their reactivity (i.e. how accessible atoms are for collisions). There are many possible methods to arrange bonded atoms in space. For example, the atoms could simply bond at the position they collide. However, the resulting shape of the molecules in the system could lead to collisions between atoms that should not be possible. Moreover, in reality, atoms bond together in well-defined energy-efficient configurations. To ensure a more uniform representation, all atoms that bond to or break from another are rearranged to represent these energy-efficient configurations. The heaviest atom bonded is used as a reference to decide which one must remain fixed in space and the others are moved according to that position. So, when an atom at the end of a big molecule gains or loses a bond, only the atoms that form the lighter part of the molecule are repositioned. Repositioning the atoms this way facilitates the recognition of molecules from visual information. Two molecules with the same bonded atoms will be represented identically; the only possible difference is the orientation of the molecule in space. Since atoms are not permitted to move relative to each other to simplify calculation, the repositioning is necessary. This also implies that rotational degrees of freedom are not currently implemented.

In the simulator, the carbon and nitrogen have each three valences and oxygen has two. Carbon valences were reduced, instead of the four naturally found, to avoid overlapping problems in the two-dimensional representations. However, to ensure a

different reactivity for the carbon atom, the dissociation energies of bonds with the latter are different from the nitrogen atom.

1.3 Results

Several simulations were done with the current version of the simulator to evaluate its similarities with respect to classical physics and chemistry, as well as to explore emergent phenomena. The first experiment demonstrates that the system can reach equilibrium in terms of the kinetic energy distribution. The second experiment shows that it can also attain dynamic chemical equilibrium and adapt to a chemical perturbation. The third experiment demonstrates that the simulator enables flexible energy modulations that influence the behavior of the system. Finally, the fourth experiment shows that different molecules can dynamically emerge from the chemistry. The first three experiments use 800 molecules of dihydrogen (H_2), for a total of 1600 atoms. For the last experiment, the number of atoms is set to 800 distributed with 40% of carbon, 20% of nitrogen and 40% of oxygen. Each valence of all atoms is bonded with hydrogen, for a total of 2898 atoms.

1.3.1 First experiment: Statistical distribution of particle speeds

The simulator uses Koenig's theorem to compute kinetic energy distribution between moving particles during a collision. Upon equilibration of a simulation, the distribution of particle speeds should thus obey Maxwell-Boltzmann statistics (for more informations on Maxwell-Boltzmann, see [25]). For a two-dimensional system, the normalized probability density function is derived as

$$f(v) = \frac{mv}{kT} e^{-mv^2/2kT} \tag{1.11}$$

where k is the Boltzmann's Constant (defined as 1 in Eq. 1.11) and T is the virtual temperature of the system. Speed (v) is defined as

$$v = \sqrt{v_x^2 + v_y^2} \tag{1.12}$$

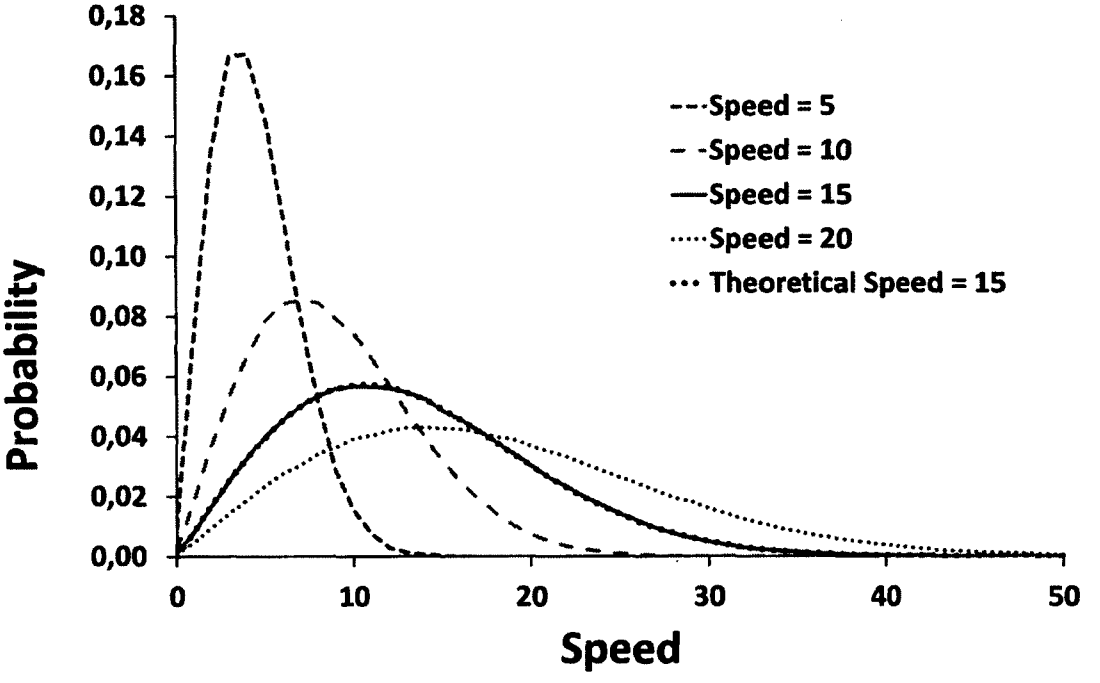

Figure 1.3: Molecular speed probability distribution. Only one theoretical result is shown to simplify the graph.

The average speed $\langle v \rangle$ is

$$\langle v \rangle = \sqrt{\frac{\pi kT}{2m}} \tag{1.13}$$

The first experiment was designed to confirm this behavior. For the simulations, chemical reactions were deactivated. Simulation was run using 800 H_2 molecules. Molecules were initially given random velocities, but identical speeds. Four simulations were done with initial speeds of 5, 10, 15 and 20. The simulations were each run for 20000 iterations. It takes approximately 1000 iterations to attain stabilization of the speed distribution. At thermal equilibrium (iterations 1000-20000), the speed distribution obeys perfectly Maxwell-Boltzmann statistics, as illustrated in Fig. 1.3. A theoretical distribution was plotted for an initial velocity of 15. For the simulated distribution, the temperature was defined using the average speed relation

$$T = \frac{2m\langle v \rangle^2}{\pi k} \tag{1.14}$$

where $\langle v \rangle$ was defined as

$$\langle v \rangle = \sum_i \frac{n_i v_i}{N} \tag{1.15}$$

where n_i are the relative occurrence of the speed v_i and N the total number of particles.

1.3.2 Second experiment: Dynamic Chemical Equilibrium

The first experiment demonstrates that the simulation, from the point of view of kinetic energies, can attain thermal equilibrium that obeys Maxwell-Boltzmann statistics. The second experiment was thus devised to validate that the simple model for bonding and internal energies, defined in the simulator, could reproduce dynamic chemical equilibrium, as expressed by the Le Chatelier's principle. This principle states that if a chemical system in dynamic equilibrium is disturbed by changing the conditions, the position of the equilibrium moves to counteract and to dissipate the effects of the perturbations (for more informations about Le Chatelier's principle,

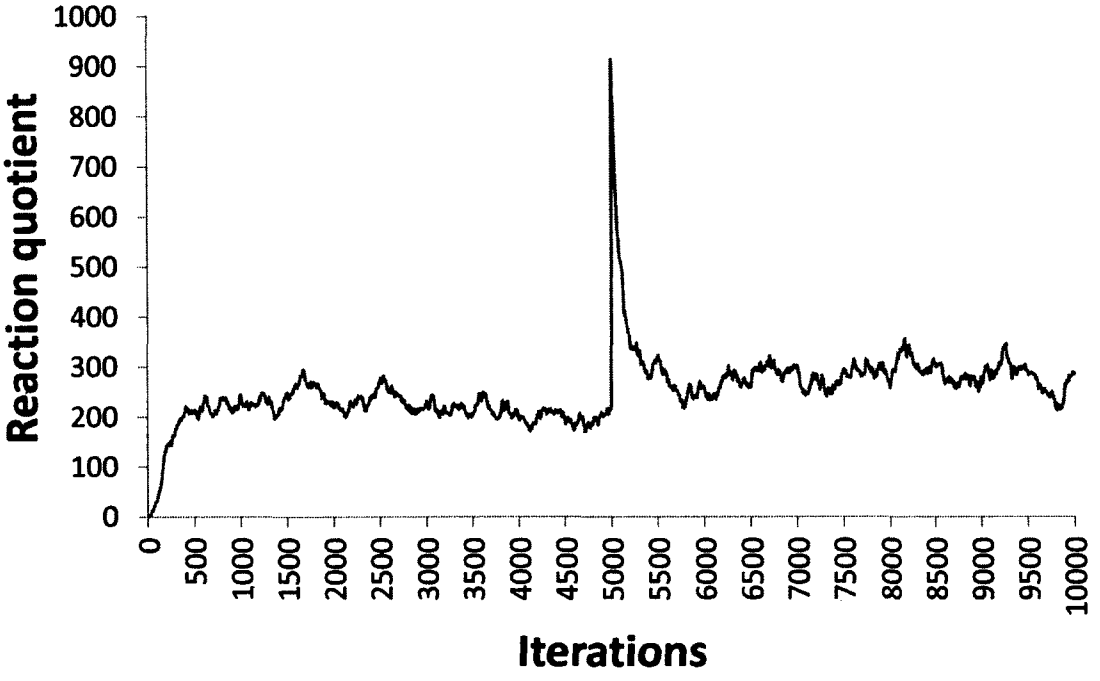

Figure 1.4: Equilibration of the reaction $2H \leftrightharpoons H_2$. At 5000 iterations, 400 hydrogen atoms were added.

see [25]). This simulation was again run with 800 initial H_2 molecules, but with the chemical model activated. The simple dihydrogen dissociation reaction ($H_2 \rightleftharpoons 2H$) was thus studied. The reaction quotient for this reaction is defined as $Q_r = [H]^2/[H_2]$ where $[H]$ and $[H_2]$ are, respectively, the number of hydrogen atoms and the number of dihydrogen molecules. The simulation was run for 5000 iterations. The results (Q_r vs time) are illustrated in Fig. 1.4. The system reaches chemical equilibrium after 750 iterations, as the reaction quotient becomes stable. To perturb the system, free hydrogen atoms were added after the 5000^{th} iteration and the simulation was resumed. Initially, a drastic increase in Q_r is observed. As the simulation progresses, the system evolves towards a new equilibrium to counteract the perturbation. After 10000 iterations, the system has shifted to a new equilibrium near the initial one.

This experiment clearly demonstrates that the system can reach dynamic chemical equilibrium and adapt to perturbations. The simple chemistry model defined in this simulator thus reproduces the Le Chatelier's principle, even if it has not been explicitly defined. It is a result of all the interactions combined with the energy driving the system to a stable equilibrium and it demonstrates, with the results of the first experiment, that the chemistry model is self-consistent and coherent.

1.3.3 Third experiment: Energy influences on the system

As explained previously, the artificial chemistry defined in the simulator is driven by energy (kinetic, internal, bonding) constraints. Modifying the total energy of the simulation should influence the kinetic and chemical behaviors of the atoms and molecules. To show the flexibility of the grid editor and demonstrate that the energy has an influence on the system, the third experiment uses a grid with a side that cools atoms (decreases their kinetic energy) bouncing on it and the opposite side that heats them (increases their kinetic energy). Simulation was run ten times using 800 H_2 molecules with deactivated chemistry. Since the atoms are randomly and uniformly positioned on the grid, the number of atoms by row and column in the grid is initially evenly distributed. After 5000 iterations, a condensation phenomenon is observed on the side that cools atoms. Fig. 1.5 shows the average initial quantity of atoms per column into the grid and the average quantity after 5000 iterations.

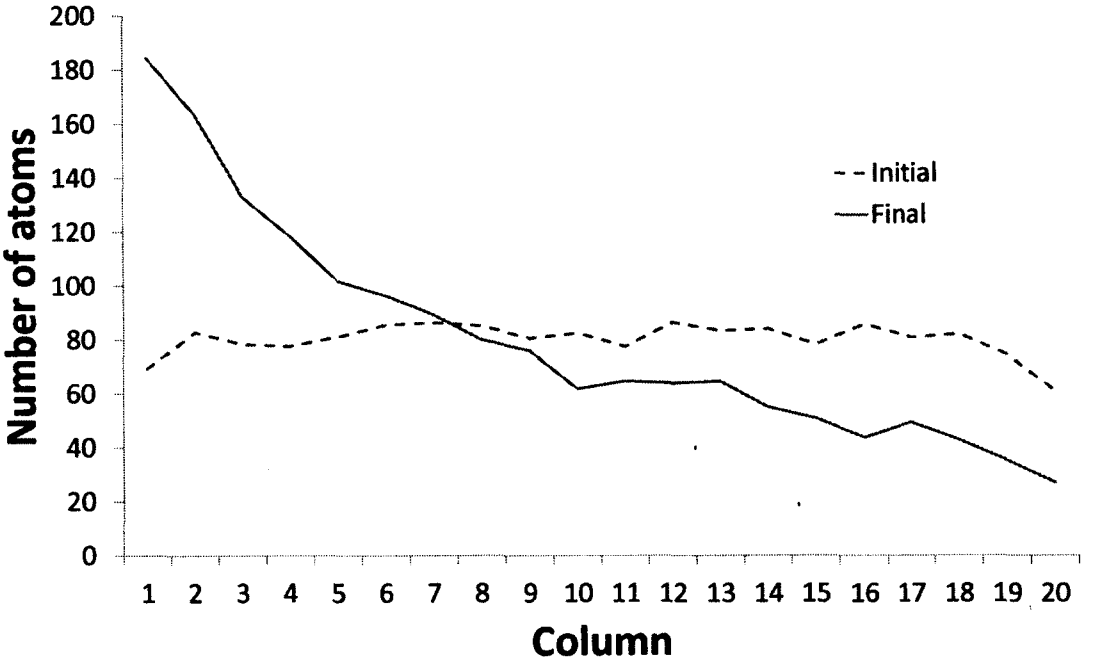

Figure 1.5: Partitioning of atoms in each column of the simulator grid. The grid has 20 columns and 20 rows. The left column cools the system, the right column heats it.

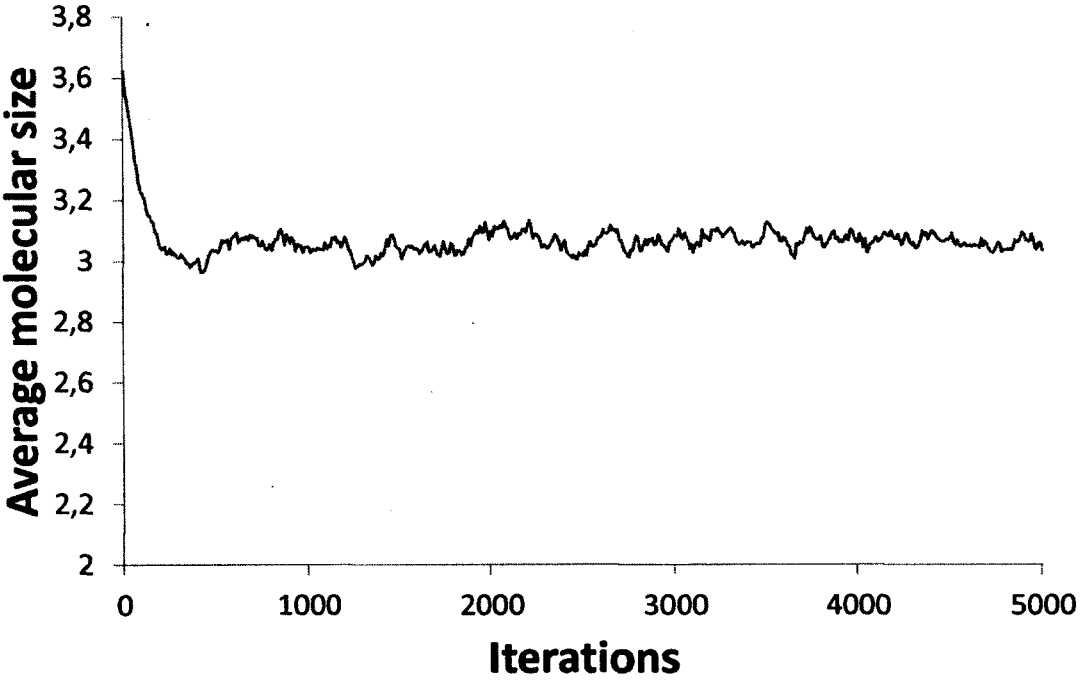

Figure 1.6: Average molecular size over time. As collisions occur, molecules are broken apart until chemical equilibrium is attained.

The results show clearly that the majority of the atoms are positioned into the left columns.

1.3.4 Fourth experiment: Emergence of molecules

For the final experiment, the simulation involves all atom types defined in the simulator (i.e., H, C, N, and O). The simulation is initiated with predefined proportions of these atoms with their valences completely filled with hydrogen atoms (i.e., CH_3, NH_3 and H_2O). At first, as collisions occur, these initial molecules are broken apart into smaller fragments. From these simple portions, larger, more complex molecules arise. Bigger molecules are inherently more collision prone and therefore, their chance of being broken apart increases, producing more building blocks for others, more stable molecules. With the results of the third experiment, when condensing molecules,

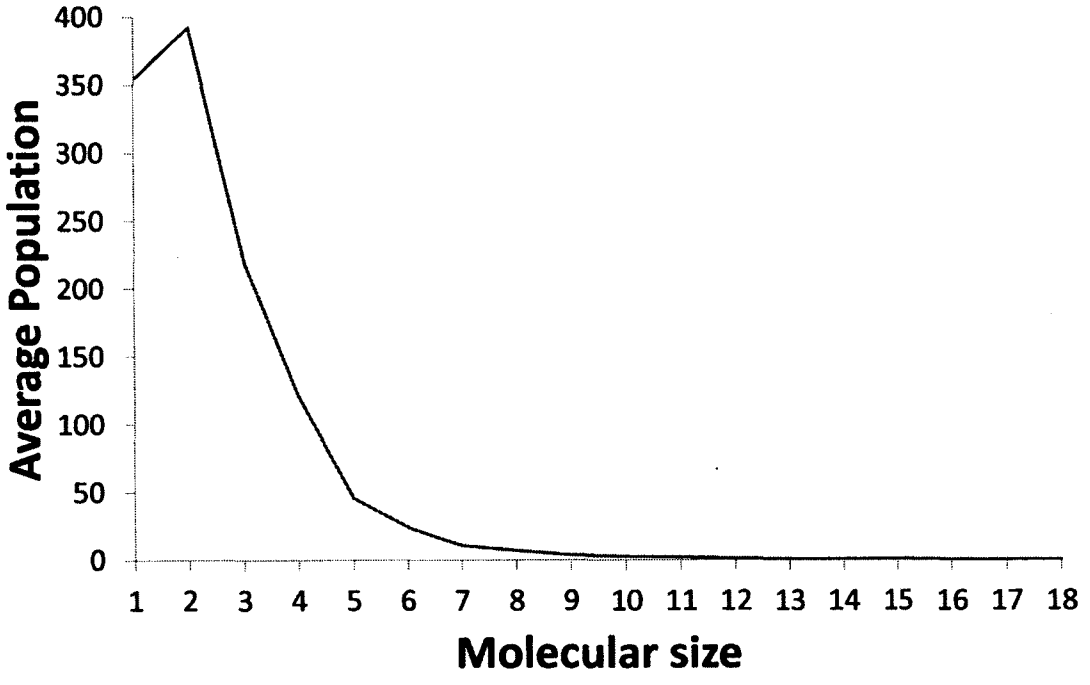

Figure 1.7: Average molecular population. Smaller molecules tend to accumulate more in the system than bigger ones.

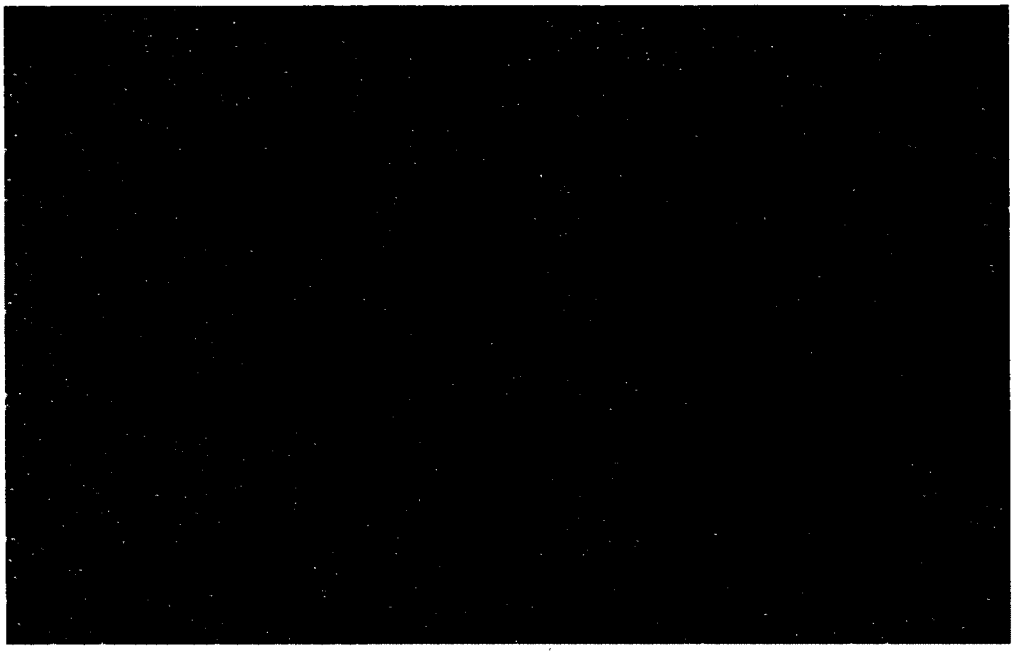

Figure 1.8: Emergence of complex molecules. Bigger and more complex molecules emerge from simple initial conditions. Hydrogen (white), Carbon (gray), Nitrogen (blue) and Oxygen (red).

the available energy reduces their chances to be broken. After 750 iterations, an apparent chemical equilibrium is attained, and the molecular average size appears to be constant (Fig. 1.6) which is coherent with the second experiment. Fig. 1.7 shows the average distribution of molecules with respect to molecular size, regardless of atomic composition. The size of a molecule is represented by its number of atoms. Fig. 1.8 shows a portion of a simulation. Bigger molecules emerged from simple initial molecules. Dihydrogen molecules have naturally appeared from free hydrogen atoms as a result of prior collisions.

1.4 Discussion

The simulator and the artificial chemistry described in this work represent a simple, yet reasonable approximation of reality. As demonstrated in the four experiments,

realistic physical and chemical behaviors, not explicitly defined, emerged from this simulator. In relation to actual chemistry, properties emerged and were observed. Molecules spontaneously appear from the original blocks and patterns do emerge. The artificial chemistry is therefore constructive.

The transition from simple molecules to self-replicating ones could eventually be achieved with the presented artificial chemistry. At the present moment, there are some restrictions on the type of molecules that can emerge. As explained previously, an atom can only bond to another if they are not already bonded together, directly or indirectly, thus preventing formation of cyclic molecules. This restriction is only due to the current implementation of the control of geometry of the molecules in the simulator, not the chemistry itself. Although cycle formation is interesting, it is not mandatory to observe emergent phenomena; it simply has not been implemented yet in order to speed up the simulator development. It is a feature that will be added in a future version of the simulator.

The simulator currently uses a hard sphere scheme for collisions between atoms. This model is an excellent approximation in the context of the simulator. There are some other schemes that exist to simulate collisions on an atomic scale, like quantum mechanics. Unlike Newtonian mechanics (and thus hard sphere collisions), quantum mechanics is more complex and more computer intensive. Furthermore, there is no need for such precision with the presented artificial chemistry, because it is only an approximation of the reality, not the reality itself. Another interesting scheme for collision and motion that is valid with Newtonian mechanics is a force-driven simulation. A force-driven simulator could bring interesting add-ons to the artificial chemistry. For example, partial charges could be added on molecules and atoms to influence their motions and positions. With partial charges, surface tension could be modeled as well as hydrophobic phenomenon. This change in the way the atoms move does not, however, influence the specification of the artificial chemistry. Moreover, partial charges could lead to additive non-covalent (non bonding) attractive interactions between molecules, and lead to self-assembly phenomena, bridging the gap between small molecules and biochemical systems.

The actual implementation of motion uses simply the product of velocity and time to move atoms. Since acceleration is null, this method gives excellent results and is

accurate. The need for a better integrator will appear only if acceleration changes, for example when forces will be added. However, modification of the simulator will not affect the artificial chemistry and its underlying simple rules.

1.5 Conclusion

We have developed a new artificial chemistry simulator that is controlled by the energetic properties of the atoms in the system. With this initial version, it is already possible to observe the emergence of different molecules than the ones involved initially. The use of energy considerations allow a better control of the interactions between atoms than just states and type constraints, and thus represents more accurately actual chemistry. The reaction rules are simple and similar to what is found in nature. We have shown that our simulator is self-consistent, coherent and exhibits emerging behavior similar to chemistry. There are many parameters that can be modified in order to obtain different molecular results and these are what makes the richness of our simulator.

Chapitre 2

Un système cardiorespiratoire pour un patient virtuel

Résumé

Cet article présente un nouveau simulateur d'un système cardio-respiratoire pour un patient virtuel. Ce simulateur est utilisé à l'intérieur d'un jeu sérieux afin d'appuyer la formation du personnel médical, principalement les infirmiers et infirmières en traumatologie. Le simulateur s'exécute en temps réel et permet, à l'aide de mécanismes simples, de représenter différentes maladies et blessures. Le simulateur peut réagir adéquatement lorsqu'un infirmier ou une infirmière effectue une action afin de stabiliser le patient. Le patient virtuel est modélisé à l'aide d'une approche dite ascendante (bottom-up) en n'utilisant que des interactions de base entre les composants du système afin d'obtenir des comportements complexes.

Commentaires

Cet article s'inscrit dans le cadre d'un projet beaucoup plus large chapeauté par le GRITS (Groupe de recherche en innovation techno-pédagogique en santé). Le but du groupe est d'utiliser les nouvelles technologies dans la formation des intervenants en sciences de la santé, entre autres à l'aide d'un

jeu sérieux. Ce logiciel sera basé sur le simulateur que j'ai développé et qui est présenté dans cet article. J'ai effectué le développement complet du système circulatoire et respiratoire du patient. J'ai écrit l'article en totalité, en plus d'effectuer tous les tests présentés. L'article a été soumis et accepté à la conférence ECAL2013 (European Conference on Artificial Life 2013).

Précisions sur l'article

Le simulateur présenté dans cet article est utilisé avec un moteur de jeu vidéo. La vitesse d'exécution du code est donc assez rapide pour répondre adéquatement aux différentes actions posées dans le jeu. Les formules utilisées dans le simulateur sont assez simples et rapides à calculer et permettent d'obtenir un rendement supérieur à 60 images par secondes.

Les deux systèmes présentés sont fonctionnels. L'architecture étant modulaire, il est assez simple d'ajouter des systèmes supplémentaires. Cependant, comme plusieurs systèmes importants, tel que le système nerveux, ne sont pas encore totalement développés et intégrés, les capacités du simulateur restent limitées. L'article explique cependant comment le patient réagit à certains stimuli telle qu'une coupure ou un changement dans l'atmosphère.

Il est aussi possible de spécifier certains problèmes sur le patient, comme des coupures par exemple. Certaines maladies, tels que divers types de problèmes cardiaques peuvent aussi être intégrées en modifiant le rythme de battement du coeur. Ces déstabilisations très simples peuvent être spécifiées à l'aide du fichier XML servant à représenter le corps humain du patient. Le simulateur réagit adéquatement lorsque les systèmes sont déstabilisés.

A cardiopulmonary system for a virtual patient

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Keywords: Biological simulation, virtual patient, cardiovascular model, respiratory model

Abstract

We present a simulation of a cardiopulmonary system. The simulation is used within a serious game to help for nurses education. It runs in real-time and can be easily modified to represent different illnesses. The system can adequately react when a nurse executes an unexpected action on the patient. The simulator uses a bottom-up design to model the cardiopulmonary system, using simple mathematical models and basic interactions to reproduce high-level and complex behaviors.

2.1 Introduction

Simulation is a good way to learn and practice in a safe environment. The simulation provides useful feedback to help students and trainees to learn from their mistakes. However in healthcare, most of the simulations and simulators require actors or mannequins [23, 30] to practice on. Since these simulations are expensive to use and can not be installed everywhere, it is hard for a student to practice anywhere else than schools and hospitals. Furthermore, most of these existing simulations for nursing education require the supervision of a technician or the use of a lot of parameters, which are often difficult to handle for an inexperienced user. Virtual simulations for nurses' training already exist [15, 41]. However, most of them lack realism or tools needed by a teacher to provide useful and complete simulation for nursing students. To solve these major inconveniences, we propose a serious computer game coupled with a simulator that relies on interactions of simple components to reproduce complex behaviors. The model of the virtual patient is simplified and based on biological and physiological behaviors. It only specifies atomic parts of the complex system and the basic interactions between them. From these interactions, the required complex behavior emerges and can be studied. This innovative approach will help nurses taking charge of poly-trauma patients at the hospital. Given the low frequency of certain clinical situations in critical care, the use of computer simulations to develop and maintain skills is very well-advised. This active and autonomous learning mode, exercised in a virtual world, will facilitate the transfer of skills in real-life situations. In the context of a shortage of clinical placement for nursing students, the computer simulation becomes a valuable tool within the reach of educational and health institutions to improve healthcare quality and patient safety.

The human body is a very complex system. Reproducing a perfectly accurate simulation of the human body would require a huge amount of computational resources and a perfect understanding of the underlying physiological processes. This is therefore an uneasy task if not, an impossible one. However, there are many efforts made to construct standards [8, 6] and common parts [10] that could be used for a unified model of the human body. More realistic approaches, based on mathematical models like HumMod [16], are also developed. The mathematical approach of

HumMod contains many variables and use complex formulas that represent the final behavior of the entire system. These models are very precise and require a good understanding of the underlying physiological processes. Researches in physiology and bioengineering are currently conducted to find these mathematical representations. One of the underlying objective of the presented simulator is to reproduce high level behavior without explicitly defining all possible interactions in the system with high level formulas used by these more classical mathematical models.

Most of the models developed for human body simulation use physiological and physical approaches to obtain adequate simulation [2, 27]. Some of them are slow to compute results, mainly due to the complexity of the formulas they used. Since the simulations must execute in real-time within a game engine, these models can not be used. The proposed model relies on such physiological and physical concepts. However, instead of representing complex interactions and using time-consuming computations, the system only uses basic physics formulas for on localized components, making it faster to compute.

In this paper, we present the cardiopulmonary system developed for the serious game used during the training of nurses. The next section describes the simulator and each of its subsystems. The third section shows some results of the simulator and a discussion about the simulator is presented in the fourth section.

2.2 Simulator description

Our current version of the simulator models the cardiovascular and the respiratory systems. Each system is modeled after its biological functions. The simulator runs in real-time and can thus be linked to a game engine in order to simulate an emergency room with an injured patient. Each of the modeled systems is a simplification of the reality but its behavior is consistent with the physiological response of its human counterpart.

The update process of the simulator relies on the game engine. The game engine updates the simulator periodically using a time step (Δt). Each system is updated accordingly to that time step by the simulator. For each update of a system, all its sub-components are also updated using this time step.

2.2.1 Body definition

The simulator relies on a XML file to describe the human body. The entire body description is decomposed into different systems, i.e. cardiovascular, respiratory, nervous, muscular, etc. This paper emphasizes only the description and the simulation of the cardiovascular and the respiratory system. Each system is viewed as a list of connectibles and a list of organs. Each connectible represents the media used for information transfer. Connectibles are grouped in subsets representing logical unit of information diffusion. For example, the blood vessels and how they connect to each other in the right arm will be specified as a subset for the cardiovascular system. In the cardiovascular system, the connectible are called blood vessels. In the respiratory system, they are airways and alveoli. Each connectible can be linked to other connectible to create a circuit. Each subset can also be linked to others, creating a more complex circuit for information diffusion. A connectible can be split into sections of equivalent volume. Each of these sections contain a part of the body fluid that moves into the connectible. For the circulatory system, it is a blood part. Each fluid part contains different metabolites (see the metabolites section for the definition). Fig. 2.1 illustrates the different compounds of a system for the circulatory system. The use of XML file to specify the different values used by the model have many advantages. Among others, it can be easily modified and it is simple to understand. Since the simulator is used for nursing education, the XML specification is also an easy mechanism to specify injuries to the patient and to create new scenario and cases to practice on.

2.2.2 Circulatory system

One of the main system of a human body is the cardiovascular system. The blood flows through the body, diffuses nutrients to various organs and retrieves waste produced by cells. Most of the non-nervous signals of the body use the cardiovascular system to reach their area of action. In the simulator, a virtual bloodstream is used as a transporter and is composed of two circulation loops. The first one is the pulmonary loop. The blood flows from the right ventricle of the heart to the lungs and returns back into the left atrium. The second is the systemic loop. The blood flows from the left ventricle of the heart and returns back into the right atrium after

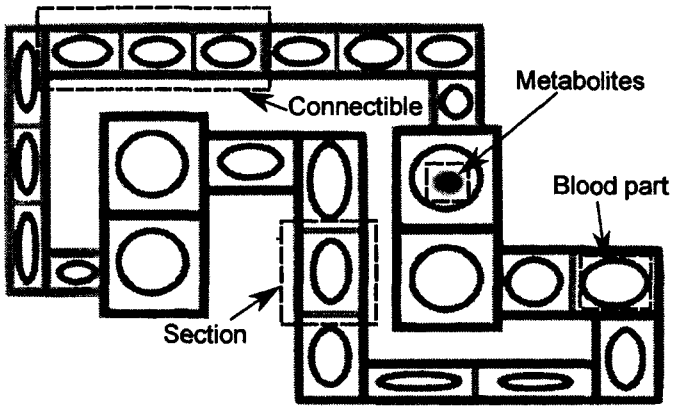

Figure 2.1: Simplification of the circulatory system to illustrate its different compounds. Each main color represents different subsets of connectible. The outermost bold rectangles are blood vessels (connectible). Inner rectangles are sections. Blood part (red circle) can contains different metabolites (purple circle). Blood vessels are linked together.

passing through the different parts of the body. The blood flows in blood vessels, creating a delay between the emission of the signals (like hormones) and the start of the associated effect. At the beginning of the systemic circulation loop, the blood vessels, called arteries, divide into smaller vessels. They subdivide until reaching the capillaries bed, modeled as a large container of blood to simplify the simulation. In these capillaries, nutrients contained in the blood can diffuse to irrigated organs. The waste produced by the organs are diffused into the blood of the capillaries. The blood then continues its way back into other blood vessels, called veins. The veins merge together on their way back to the heart. These splitting and merging of blood vessels mix the content of the blood to ensure a better repartition of metabolites into all systems of the body. It is also mimicking very well the human circulatory system since blood vessels also split and merge in the same way. Fig. 2.2 shows the schematic view of the cardiovascular system.

Each blood vessel, as a connectible, is divided into sections containing different blood parts, each of them having some metabolites. When the simulator updates the cardiovascular system, each blood part flows through its vessel following the pressure gradient between that part and the next one in the vessel. In the simulation,

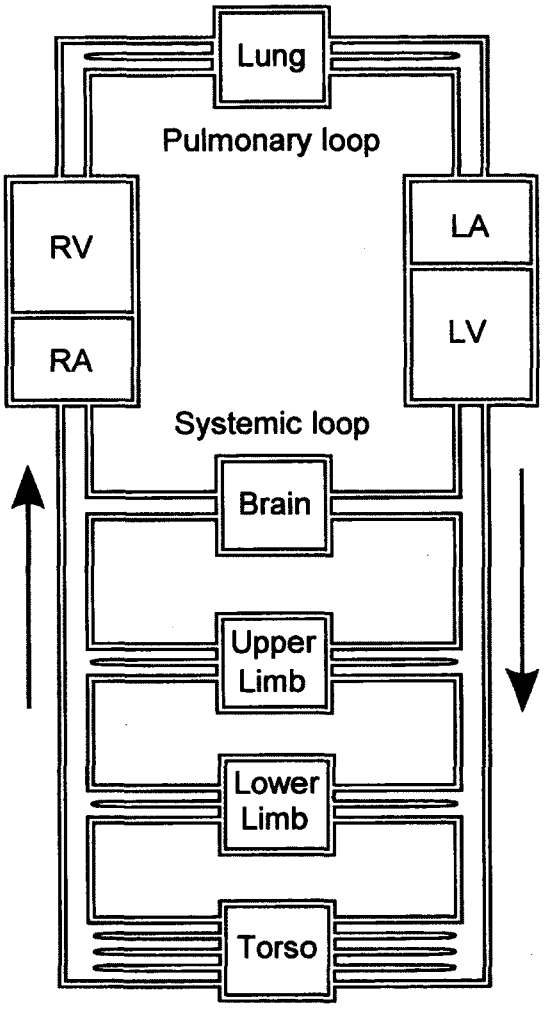

Figure 2.2: Schematic view of the cardiac model. LA and LV designate respectively Left Atrium and Left Ventricle. RA and RV designate respectively Right Atrium and Right Ventricle. The central boxes of the figure (i.e. Brain, Upper Limb, etc.) represent different connectible subset of the system. The subset contains arteries, veins and capillaries.

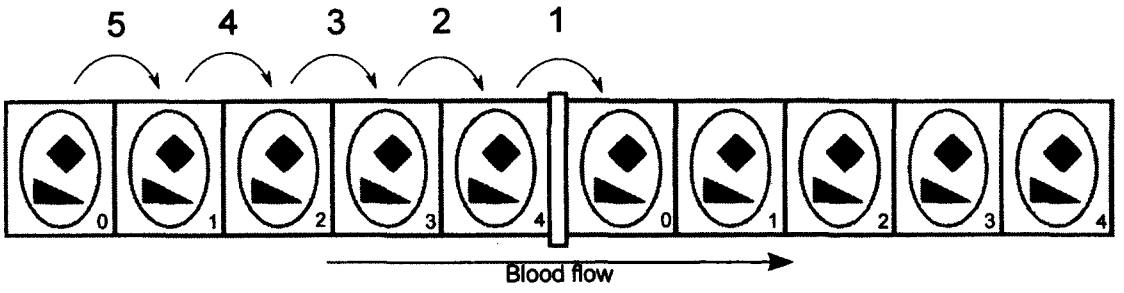

Figure 2.3: Schematic view of the update in blood vessels. The blood flows from left to right. In this example, each blood vessel contains five sections. Step 1 of the update process moves a certain quantity of blood from the last section of a vessel to the first section of all the next blood vessels, using Eq. 2.1. Then, step 2 to 5 move a certain volume of each other blood part to the next blood part in the vessel. This circulation of blood is executed in reverse order (from the last section to the first). It avoids transportation of new metabolites through all the blood parts of the blood vessels.

each vessel is represented by a length (L) and a radius (r), thus modeled as a finite cylinder. This implies that each section of a blood vessel is also modeled as a cylinder of the same radius as the blood vessel but with a length of L/n for a vessel of n sections. To reproduce the pulsative flow of the blood, other simulations are based on the Windkessel effect, like [38, 40]. The proposed simulator however relies on the standard Hagen-Poiseuille equation (Eq. 2.1) [11, 28, 14] to calculate the volumetric flow rate (ϕ_i) in each blood vessel section i during a time step. The pulsatile work of the heart will impact the Eq. 2.1 by varying the pressure in a blood vessel section for a particular time step. The volumetric flow rate using the Hagen-Poiseuille equation is

$$\phi_i = \frac{\pi r_i^4 (P_i - P_{i+1})}{8\eta L_i} \tag{2.1}$$

where r_i and L_i are respectively the radius and the length of the i^{th} blood vessel section in which the blood flows. P_i and P_{i+1} are the pressure of the blood in these sections and η is the dynamic viscosity of the blood. The length of a blood vessel section remains constant through the simulation. The pulsatile flow produced by the heart must be damped. In the human body, the elasticity of the blood vessel is

responsible for this damping. To mimic this behavior in the simulator, we propose a model inspired by Hook's law of elasticity. The difference in volume between the actual volume of the blood part and the relaxed volume of the blood vessel section replaces the displacement value in Hook's law. An adjusted elasticity constant (k) is used, which can be specified for each blood vessel. The pressure P_i in the blood vessel section i is given by

$$P_i = \frac{k(V_i - W_i)}{2\pi r_i L_i} \tag{2.2}$$

where V_i is the volume of blood in the i^{th} vessel section and W_i is the relaxed (initial) volume of that blood vessel section. The resulting change in pressure at each time step influences the volumetric flow rate given by the Eq. 2.1 of the next time step.

During a time step (Δt), all blood parts circulate throughout the sections of each blood vessel using the volumetric flow rate as explained previously. The new blood volume $V_i^{'}$ in each section i is represented with

$$V_i^{'} = V_i - (\phi_i - \phi_{i-1})\Delta t \tag{2.3}$$

The blood part circulation is performed in reverse order. It is a design choice that required less memory than moving the blood parts in the way they flow. The simulator do not have to keep an entire copy of each blood parts until the end of the update pass. The Fig. 2.3 shows the different steps to flow the blood through each sections of blood vessels. Each transferred blood part contains the same metabolites, in the same ratio, as the initial blood part they came from. Since volume changes at each time step, the blood flow is constantly recalculated.

As explained, the capillaries are modeled as a large container. In human body however, capillaries are large network of very small blood vessels. This arrangement of blood vessels induces a great resistance to blood flow due to the small radius of these vessels. The Eq. 2.1 can be rewrited as

$$\phi_i = \frac{(P_i - P_{i+1})}{R_i} \quad with \quad R_i = \frac{8\eta L_i}{\pi r_i^4} \tag{2.4}$$

where R is the resistance to blood flow of the blood vessel. In the simulator, since the capillaries are modeled as a large container, the resistance of the container must be adapted to represent more accurately the resistance of a network of blood vessels. Each capillaries container has a number of sub-vessels (n). Each of them are identically modeled with a radius of 10 micrometers and a length proportional to the volume of blood of the entire capillaries container and the number of sub-vessel it contains. The model considers the sub-vessels in capillaries to be parallel, thus lowering the total resistance R_i, calculated with

$$\frac{1}{R_i} = \sum_{j=1}^{n} \frac{1}{R_j} \tag{2.5}$$

where R_j is the resistance in a sub vessel of the capillaries. Since all the R_j are identical, Eq. 2.5 can be simplified by

$$R_i = \frac{R_j}{n} \tag{2.6}$$

This model simplifies the blood flow in large and complex network of blood vessels in capillaries while keeping the physical incidence of their small radius on resistance.

To instill a pressure gradient to the bloodstream, the blood must be pumped. This role is devoted to the heart which is made of four parts. There are two atriums in which the blood arrives from the different circulation loops and there are two ventricles that pumped the blood out of the heart. The left atrium receives blood from the pulmonary loop while the right atrium receives it from the systemic loop. The simulated heart has also two group of self-polarizing cells, called sinoatrial node (SA node) and atrioventricular node (AV node). These nodes polarize and depolarize themselves to conduct the contraction of atriums and ventricles. For more details on heart nodes and their mechanisms, see [14, 28]. In the simulator, the polarization process goes through three different phases, as in reality. The first phase of the SA node is the pacemaker. The pacemaker is a slow increase of the polarization of the node. The pacemaker phase is followed by a rapid depolarization until the maximum is reached. This abrupt depolarization emulates the sudden increase of ions (charged metabolites) that transfer through the membrane of the cells in a real heart. The

contraction of the atriums happens at the end of that phase. Finally, the third phase is the repolarization until the minimum value is reached and the cycle restart. During the pacemaker phase, the atriums relax and retrieve their original volumes. The AV node follows the same process. However, when the SA node reaches its maximum polarization value, the node sends a signal to the AV node. That signal disturbs the pacemaker phase of the AV node and initializes the rapid polarization. The contraction of the ventricles occurs when the polarization of the AV node reaches its maximum value. The relaxation of the ventricle follows during the pacemaker phase of the AV node. This depolarization/polarization, which is only an exchange of charged metabolites (mainly of sodium and potassium) between the membrane of the cells forming the heart, is simplified for the simulator.

This level of details for the heart's implementation, using polarization levels, allows a better control over its reaction to external stimuli. Instead of using a predefined timer to conduct the heart's beat and trying to find the right value for it in the simulator, the hormonal and neuronal systems can increase or decrease the different value of polarization in the nodes to change the behavior of the heart allowing it to beat faster or slower.

2.2.3 Respiratory system

The second simulated system is the respiratory system. This system is used to exchange the oxygen and the carbon dioxide between the body and the environment.

Like the human respiratory system, the virtual respiratory system has two main components, the lungs and the exterior environment. There are two lungs, and each of them is divided in different lobes. Each lobe contains alveoli in which the gases are exchanged with the blood in the capillaries. The lobes can be individually deactivated to simulate ill patients. The air enter the alveoli from the airways. The respiration control center is modeled as a timer. The rate of the respiration can be modified by changing the timer interval. It is in future plan to link this control center to a brain that will react to external stimuli, such as oxygen and carbon dioxide concentration as in real life. Fig. 2.4 shows the schematic of a lung in the system.

The air is modeled as an ideal gas (Eq. 2.7). And as a gas, it always fills all the

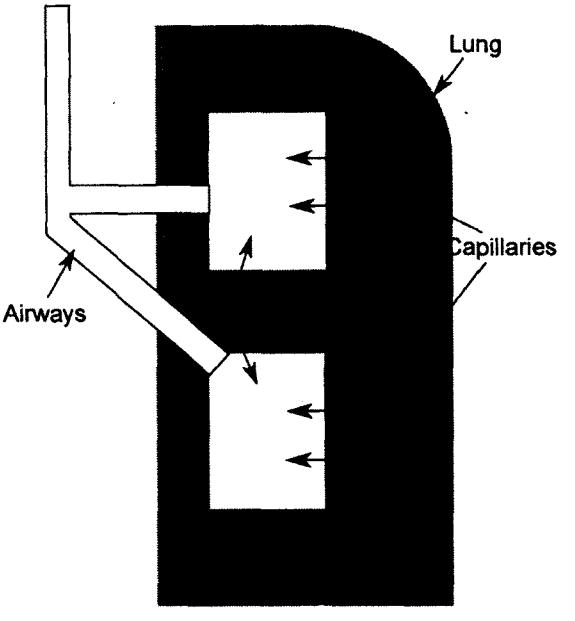

Figure 2.4: Schematic view of a simulated lung in the respiratory system. A lung is composed of lobes, each of them contains alveoli. The exterior environment is connected to the different alveoli using airways with one section. Capillaries of the circulatory system are linked to alveoli and exchange metabolites (i.e. oxygen and carbon dioxide) through gas diffusion.

available volume. The pressure P_{air} of the air depends on the volume V it fills, the temperature T in the lung, the quantity of gas (n) and the ideal gas constant R with the relation

$$P_{air} = \frac{nRT}{V} \tag{2.7}$$

The inspiration process increases the volume in the lung, while the expiration process decreases it. This difference of volume impacts the pressure of the air in the lungs, as explained by the Eq. 2.7. The air, as for the blood in the circulatory system, flows against its pressure gradient. But unlike the blood pressure, which depends of the elasticity of the blood vessels and the volume of blood it contains, the pressure of the air is calculated using the ideal gas equation (Eq. 2.7). In the simulator, the pressure of the exterior environment does not change as the respiration occurs. The air in the lung must always retrieve an equivalent pressure. Using Eq. 2.7, it is easy to find the amount of gas needed to balance the pressure between the lungs and the exterior environment. This amount of gas flows against the pressure gradient and balances the pressure in the lung at each time step.

The diffusion of gases between the blood and the alveoli of the lungs is driven by the partial pressure of these gases. However, each gas does not diffuse at the same rate. In the alveoli, all the gases composing the air are mixed together in a more complex gases mixture. This pressure of this mixture can be found using the Eq. 2.7. The partial pressure of each gas in the air can be calculated with the Dalton's law which states that the total pressure exerted by the mixture of non-reactive gases is equal to the sum of the partial pressures of each gases. For the air, the equation

$$p_i = P_{air}\frac{n_i}{n} \tag{2.8}$$

represents the partial pressure p_i of the i^{th} gas composing the air where n_i is the quantity in mole of this gas and n is the total amount of gases in the air. On the other hand, each gas dissolved in the blood has also a partial pressure. This partial pressure is calculated with the Henry's law stated as

$$q_i = \frac{n_i}{V}k_H \tag{2.9}$$

where q_i is the pressure of the i^{th} gas in the blood and n_i is the quantity of that gas in the blood. V is the volume of the blood part in which the gas is dissolved and k_H is the Henry's constant associated with the type of gas and the type of solution in which the gas is dissolved.

The diffusion of the gases takes place until the partial pressures in the air and in the blood are equal. Based on Fick's law of diffusion, the diffusion rate D_i of a gas i between the lung and the capillaries is

$$D_i = \frac{A(p_i - q_i)}{d} C_i \tag{2.10}$$

In this equation, C_i is the diffusion coefficient of the gas in the blood, A is the area of the blood vessel section that diffuses the gas, p_i and q_i are the partial pressure of that gas in the alveoli and in the capillaries and d is the distance of diffusion [14]. The quantity of gas Q_i added into the blood for a particular time Δt is

$$Q_i = D_i \Delta t \tag{2.11}$$

This diffusion process changes the respective partial pressure of oxygen in the blood and in the air of the alveoli. At the next time step, the diffusion rate changes accordingly and the cycle restarts upon equilibrium. For more information on gases diffusion in the human body, see [26].

The respiratory system is responsible for the supply of new air into the body and for the expulsion of the exhausted one. In contrast with the circulatory system which is normally closed, the respiratory system is open. This particularity allows this system to be connected with different apparatus that provide breathable air or not. They are called the exterior environment. Normally, the respiratory system is connected to the atmosphere, composed at 78% of nitrogen and 21% of oxygen with the remaining being composed of many other compounds, like carbon dioxide and water vapor. The composition of this atmosphere influences the exchange of different gases in the lungs and in the body through the partial pressure of the composing gases. A higher concentration of oxygen in the air will increase the diffusion of this gas to the blood.

When the blood flows through the organs, it exchanges the oxygen and the carbon

dioxide with them in a similar way than in the lungs. These exchanges change the partial pressure of these gases in the blood, resulting in continuous exchange when it passes through the lungs. The exchange of gases in the organs follows the same principles as in the lungs with the equilibrium of partial pressures. The major difference is that the partial pressures of the gases in organs are found using the Henry's law (Eq. 2.9) instead of Dalton's law (Eq. 2.8). It is because the gases in organs are dissolved into the cells' fluids.

2.2.4 Metabolites

All biological elements are called metabolites. Thus, every molecule that use the bloodstream or the pulmonary airways to circulate is considered to be a metabolite. It represents the oxygen, the carbon dioxide as well as the sodium, the potassium, the enzymes, the hormones and any other elements used by a system of the body. Like in human body, every blood parts, organs' fluid and air parts can contain metabolites. Instead of representing all the individual instance of a metabolite, like all atoms of oxygen dissolved in the blood, each metabolite is represented with a quantity representing the amount of individual instances. This simple representation of each set of metabolites in blood parts simplify the calculation in the different systems of the body. The pressure, the volume and the concentration, for example, can easily be found for a particular metabolite in a single blood part. The advantage of grouping all instances of the same metabolite limits the memory and the time needed to update all the systems. Furthermore, this simplification has only a small impact on the system, since it represents only a part of all instances of that metabolite in the whole body. The subdivision of the blood part and the air part allows precise control and limits actions to a specific section.

2.3 Results

The developed system must be realistic enough to be used as a simulator for nurses education. The global behavior of the system must represents the way the human body behave in similar circumstances. The first experiment validates the behavior

of the heart and the change in pressure into the bloodstream as the heart beats. It shows that cutting blood vessel to represent injuries has an impact on pressure. The second experiment validates the effect of the gases composing the atmosphere on the bloodstream. The experiment also demonstrates the effect of a ill lung to the respiratory system. The system needs 3 or 4 heart beats to stabilize at the beginning of a simulation.

2.3.1 The Work of the Heart

The heart acts like a pump. It contracts and relaxes periodically. The effect of that pump is a continuous increase and decrease of the blood pressure in the arteries. The standard values of pressure for a healthy person are between 120 mmHg (or 16 000 Pascals) at the maximum and 60 mmHg (or 10 700 Pascals) at the minimum [5]. These values represent the pressure in the blood vessels. It is the force exerted by the blood on a blood vessel wall. The Fig. 2.5 shows the pressure of the blood in the simulated aortic artery at the exit of the left ventricle. The pressure rises when the heart contracts and decreases when the blood flows out of the heart.

To simulate an injured patient, the cardiovascular system allows blood vessels to be cut. The Fig 2.6 shows the effect of a cut at the end of the simulated artery network, before entering smaller capillaries vessels. Standard pressure in these arteries is lower since resistance and elasticity damped the pulse [28]. The volume of blood that leave the blood vessel is shown as well as the corresponding blood pressure in the next connected blood vessel. This cut to the artery should be deadly if no action is taken rapidly to mitigate the problem. The virtual patient rapidly loses blood, leading to a decrease in its pressure, and possibly death. The cut is considered open and the blood escaping from the system exerts no pressure on the blood vessels or other organs. If the cut was modeled as a hemorrhage, the blood escaping the system would exert a pressure on the blood vessels, slowing the blood loss.

Another interesting feature of the simulator is the possibility to reproduce hypertension behavior. Results show that increasing the elasticity constant of a blood vessel, thus stiffening it, increases the maximum blood pressure in the neighboring vessels. Futhermore, the peak of the blood pressure in blood vessels occurs later in

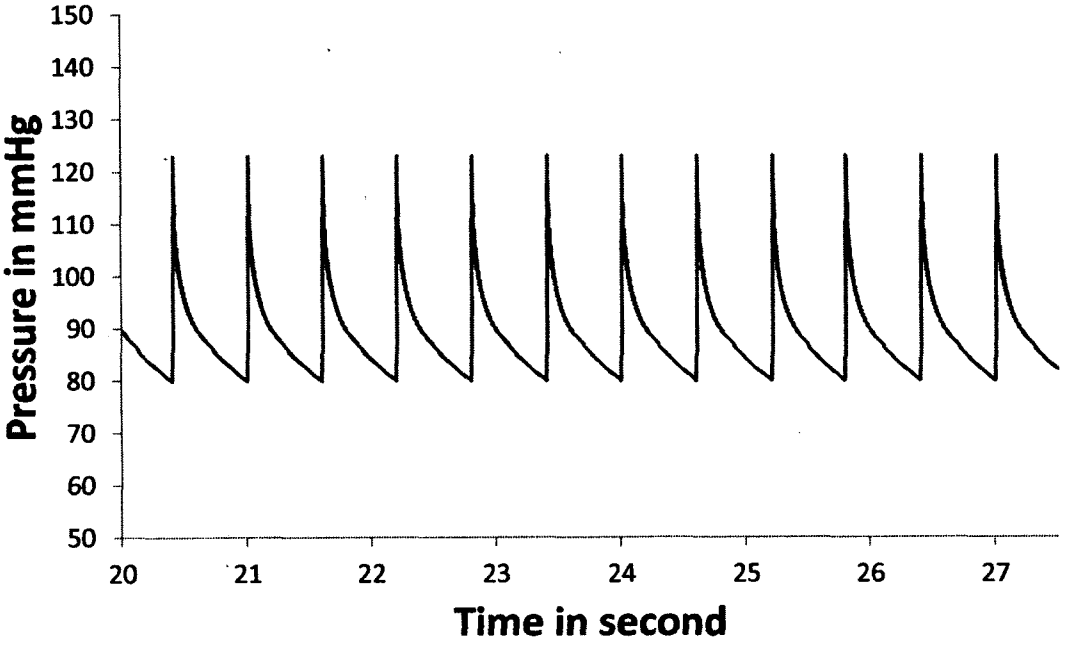

Figure 2.5: Pressure in the simulated aortic artery, at the exit of the heart. The pressure oscillates between 122 mmHg and 80 mmHg, which is in standard range for a main artery.

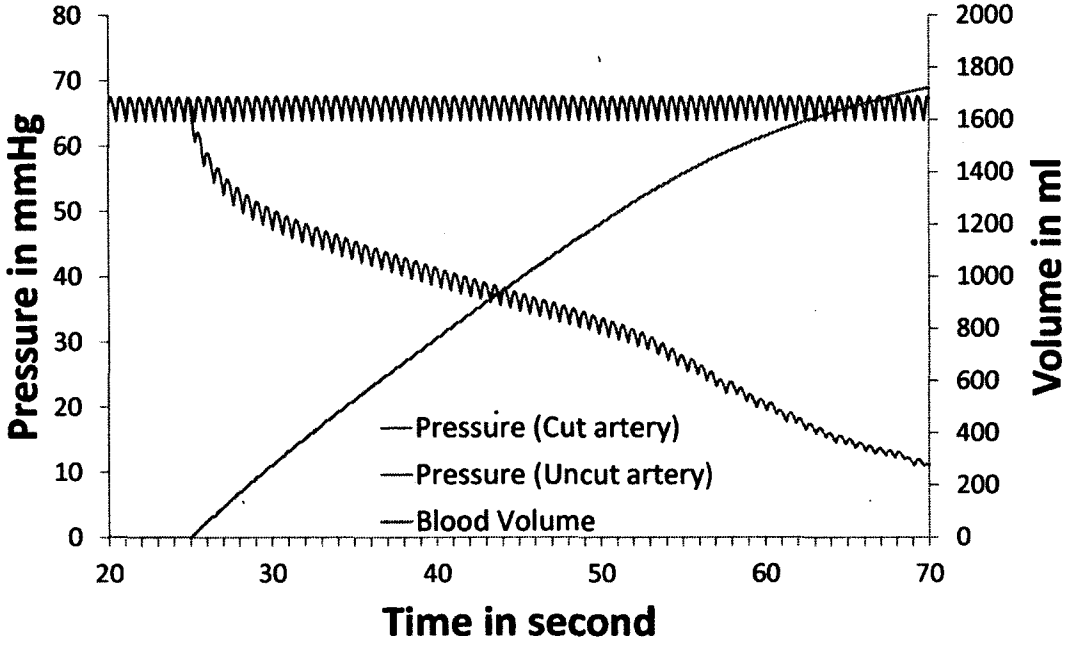

Figure 2.6: Blood pressure in a simulated artery that follows a cut. The green curve shows the volume of blood that has escaped through the cut. Red curve is the pressure in the artery when no cut is present in the system. Blue curve is the pressure in the same artery when a cut is present.

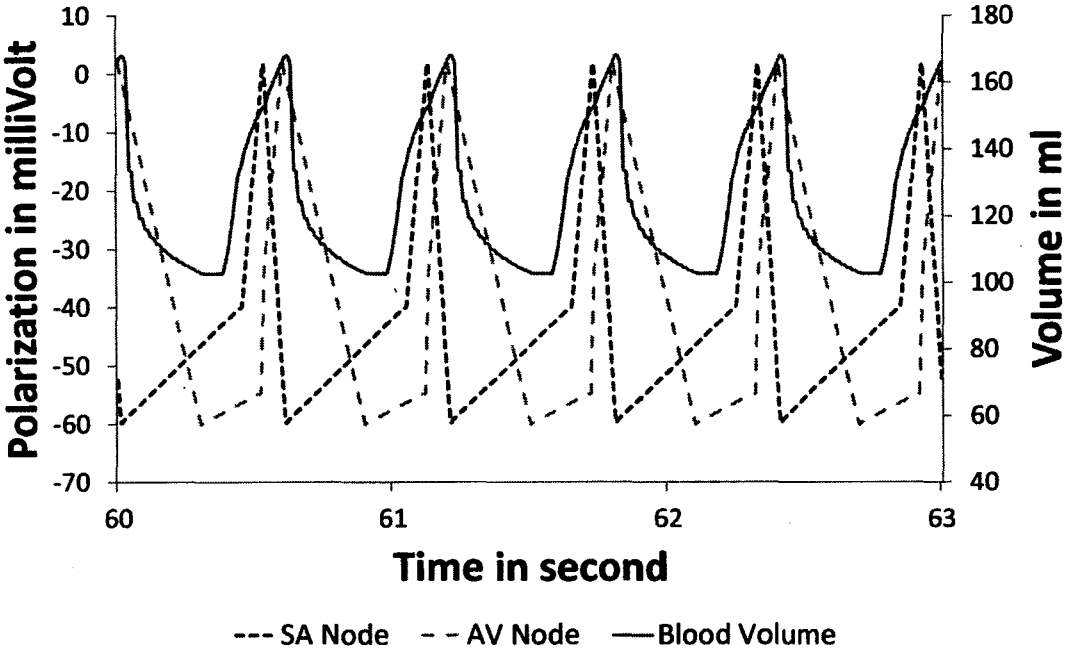

Figure 2.7: Blood volume variations of the left simulated ventricle over time. The first increase in blood represents the blood flowing from the left atrium to the left ventricle following the pressure gradient. The second increase occurs when the left atrium contracts, pushing the blood into the ventricle. The following decrease occurs when the ventricle contracts and expulses the blood into the aorta.

time with less elastic vessels, as explained in [29].

As explained previously, the heart is modeled as a pump with polarizations threshold. The pumping effect of the atriums and ventricles influences the volume of blood in the heart. The Fig. 2.7 shows the variations of the blood volume in the left ventricle of the simulated heart in relation with the polarization phases of the SA and AV nodes. The atriums contract when SA node reaches its maximum polarization value. The contraction of ventricles occurs shortly after when AV node reaches its own maximum polarization. The variation in blood volume for the ventricles is similar to the reality [28].

2.3.2 The Influence of the Air

Air composition influences the gas exchange in the human lungs. At the top of a mountain, the air pressure is lower than at sea level, which influences the partial pressure of oxygen. In the simulator, there is also a difference of partial pressure for the oxygen in the blood when the exterior atmospheric pressure changes. At sea level with standard atmospheric pressure (101 325 Pascals), the partial pressure of oxygen in the simulated blood is about 160 mmHg (104 mmHg in reality) after passing the alveoli of the lungs. At 2000 meters of altitude (70 000 Pascals), the partial pressure of oxygen in the blood is about 110 mmHg (71.93 mmHg in reality) after passing the alveoli of the lungs. The difference of partial pressure of oxygen between the simulated blood and the reality is mainly due to the absence of water vapor in the air of the simulated lungs which increases the partial pressure of oxygen, following Eq. 2.8 [28]. The absence of water vapor simplifies the process of air exchange between the exterior environment and the simulated lungs. However, the results show clearly that a difference in initial atmospheric pressure impacts the system.

2.4 Discussion

The goal of this work is to reproduce the behavior of a cardiopulmonary system. This simulator is used within a serious game for the training of nurses. One of the primary requirements of the system is a good representation of external and internal

physiological processes. The system does not represent the exact reality. However, it must be realistic enough at a high level to create an immersive environment for the nurse. The presented simulator is based on simple mathematical concepts of chemistry and physics to mimic the basic interactions and behaviors of this complex system.

The presented approach, using a bottom-up design, relies on the principle of emergence to reproduce the complex interactions needed for this kind of simulation. This is in contrast with more standard approaches used in the video games industry. In a game, simulation and artificial intelligence often use finite-state machines. They are easy to define, the interaction between each component is clear and it can normally represent most of the desired behavior. However, relying on this model for a human body simulation has many disadvantages. First, there are many systems interacting together, thus complexifying the machine and increasing the chance to forget transitions when designing it. Second, this finite-state machine would required a huge amount of memory space and adding another system in the body simulation would require a lot of efforts to connect it with the others. Finally, every interactions on the model must be planned in the design stage, which are every actions and mistakes made by a nurse in training using the simulator. Naturally, predicting every mistakes and the order in which they will be made is a virtually impossible task. All these concerns have led us to create a simulator based on simple components interacting together so that complex behaviors can emerge.

The presented model is based on the subdivision of the entire system in logical units. The approach can be related to multi-agents system, where each part of the system executes its own job and send messages to other units to influence them. The model used for the simulator sends messages mainly through the bloodstream. An interesting effect of this message sending is the delay that occurs between the time a message is sent (i.e. an hormone is produced and released in the blood) and the time it reaches its zone of effect (i.e. when it binds to receptors to activate functions).

Again, the main advantage of using this kind of approach is the ability of the system to react automatically and adequately to the numerous possible actions of the nurses. When the simulator is in an unstable state, i.e. the virtual patient has injuries, the nurse in training must execute actions to stabilize it. When the nurse

makes an action, the simulator must react adequately and it must continue running. The result of the action will impact the patient, thus reflecting what would happen in reality.

Mathematical models act in the same way as our approach. There is no need to plan every mistakes made by a nurse in the system. Actions will impact the formulas to provide new outputs. However, these models, even if they are extremely efficient and complete, can often be difficult to be divided and modeled as independent subsystem.

Modeling complex systems with simple components similar to multi-agents systems is an interesting idea that allows modularity, simplicity and speed of execution. The simpler formulas used in the presented simulator represent only basic physical interactions and are used to construct more complex behaviors. In a simulator that must reproduce global behavior instead of particular physiological principles, this modularity and simplicity of configuration offer a great advantage for both the developer of medical scenarios and the nurse in training.

2.5 Conclusion

We describe a model of a cardiopulmonary system that is inspired by biological principles. The resulting behavior of the simulator corresponds to the actual behavior of a human body, thus allowing the simulator to be used for nurses' training. The decomposition into small and simple components to see the emergence of complex behaviors is an interesting way to model the problem. The teacher can specify injuries and illness to a patient, thus simplifying the creation of new medical scenarios.

2.6 Acknowledgments

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Conclusion

Les travaux présentés dans ce mémoire ont permis, d'une part, d'ouvrir la voie à une nouvelle approche de simulation pour une chimie artificielle et d'autre part, à synthétiser et simplifier un modèle physiologique d'un corps humain pouvant être utilisé pour la formation en sciences infirmières.

L'utilisation d'une chimie virtuelle basée sur des échanges d'énergies entre les atomes lors des collisions est une idée novatrice qui permet une simulation plus proche de la réalité que les autres simulations existantes. La simplicité du modèle le rend plus utile pour l'étude de phénomènes émergents que les modèles utilisés en chimie computationnelle. Notre chimie artificielle permet d'observer plusieurs phénomènes chimiques réels, une base encourageante pour de futurs développements.

Baser un patient virtuel sur une nouvelle approche, plus simple, des mécanismes d'un corps humain a permis de développer rapidement un simulateur fonctionnel. Plusieurs maladies ou blessures peuvent être simulées et l'architecture développée permet d'ajouter rapidement de nouveaux systèmes biologiques. L'approche utilisée rend le simulateur moins complexe que s'il était basé sur des équations complexes expliquant les nombreuses interactions biologiques globales du système. Le simulateur est rapide et promet de répondre aux divers besoins initiaux de formation pour les futurs infirmiers et infirmières en traumatologie.

Travaux futurs

Les différents simulateurs présentés dans ce mémoire offrent plusieurs perspectives de recherches futures. La chimie artificielle présentée au chapitre 2 pourrait être modifiée afin de refléter plus fidèlement certains comportements chimiques et physiques. Par exemple, l'ajout de forces entre les atomes pour influencer leur mouvement pour-

rait permettre d'obtenir des comportements plus réalistes. L'utilisation des forces entre atomes enlèverait aussi l'utilité de replacer les différents atomes formant une molécule de façon à reproduire des configurations qui sont énergétiquement stables. Les forces s'occuperaient de les placer automatiquement. Cette modification permettra aussi d'observer des phénomènes nécessaires à l'apparition de la vie, comme des molécules hydrophobes repoussant l'eau servant à la création de membranes, ou encore les liaisons hydrogène entre les molécules d'eau. L'ajout d'une troisième dimension donnerait la possibilité d'avoir un quatrième lien pour certains types d'atome, ce qui créerait des molécules plus complexes et plus proches de ce qu'on peut retrouver dans la réalité. Un simulateur plus complet permettrait aussi de faire certaines études et certaines expériences sur les conditions initiales nécessaires à l'obtention de molécules bien définies comme des acides aminés, des acides gras ou des carbohydrades par exemple. Le simulateur pourrait aussi permettre de reproduire la fameuse expérience de Urey-Miller et de peut-être trouver des pistes de réponses à l'origine de la vie elle-même.

Dans le cas du patient virtuel, plusieurs améliorations restent à faire afin de rendre le simulateur pleinement fonctionnel et utilisable pour la formation en sciences infirmières. Un système nerveux central contrôlerait mieux les systèmes déjà existants en réagissant à certains stimuli. De plus, un système urinaire comprenant les reins viendrait compléter la gestion du système circulatoire en contrôlant la quantité d'eau à garder dans le sang. Ces différentes améliorations auraient naturellement un coût en terme de performance. Cependant, en utilisant les mêmes principes que pour les deux systèmes présentés, ce coût devrait être assez faible pour et l'impact serait acceptable. Le patient virtuel a été développé dans le but principal de servir à la formation du personnel infirmier en traumatologie. Le système a cependant été pensé dans l'optique d'intégrer plusieurs autres branches des sciences infirmières telles que les manipulations pré et post-opératoires, ou encore les soins intensifs.

Le patient virtuel pourrait aussi servir de base pour un projet en lien avec des créatures virtuelles [4, 35, 24]. Des créatures virtuelles ayant en plus une biochimie interne pourraient permettre de spécifier certaines fonctions objectifs plus complexes et proches des concepts biologiques.

Annexe A

Énergie de liaison

Cette annexe détaille les valeurs d'énergie de liaison utilisées dans le simulateur décrit au chapitre 1. Les valeurs représentent la quantité d'énergie requise pour briser un lien entre les deux atomes correspondant.

	Hydrogène	Carbone	Azote	Oxygène
Hydrogène	432	459	386	411
Carbone	459	346	305	358
Azote	386	305	167	201
Oxygène	411	358	201	142

tableau A.1 – Énergie de liaison entre les atomes du simulateur

Annexe A. Énergie de liaison

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