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# Substantia

An International Journal of the History of Chemistry

## Open Science

Luigi Campanella, Editor

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# *Substantia*

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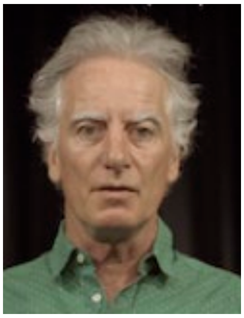

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# Preface

It is a great honour for me to write these few lines of preface to the special issues of *Substantia* dedicated to the 150th anniversary of the Periodic Table by Dmitrij Mendeleev. In 2019 there are other important anniversaries besides that of the periodic table. One of these is the centenary of Primo Levi's birth. I believe these two anniversaries are strictly related, in fact *The Periodic Table* by Levi has been considered by the *Royal Institution of Great Britain* as the "best book of science ever written". It would be sufficient to recall an impressive excerpt from "Iron", a tale of the *The Periodic Table*, to acknowledge the uniqueness of this literary work:

"*We began studying physics together, and Sandro was surprised when I tried to explain to him some of the ideas that at that time I was confusedly cultivating. That the nobility of Man, acquired in a hundred centuries of trial and error, lay in making himself the conqueror of matter, and that I had enrolled in chemistry because I wanted to remain faithful to this nobility. That conquering matter is to understand it, and understanding matter is necessary to understand the universe and ourselves: and that therefore Mendeleev's Periodic Table […] was poetry …*".

When we designed the project related to these special issues, we had in mind Levi's work and in particular his wonderful tales that belong to *The Periodic Table*. I like to recall this homage to a chemist-writer-witness to introduce the six topics that are associated to the special volumes of *Substantia*.

As President of the University of Florence which is the owner of the publisher *Firenze University Press*, I am truly grateful to the Editors – Marc Henry, Vincenzo Balzani, Seth Rasmussen, Luigi Campanella, Mary Virginia Orna with Marco Fontani, and Brigitte Van Tiggelen with Annette Lykknes and Luis Moreno-Martinez – for accepting the invitation made by the Editor-in-Chief Pierandrea Lo Nostro and for the extraordinary work for the preparation of these special issues. Of course the choice of the six subjects was not accidental: we tried to identify some features of the chemistry realm, related for several reasons to the periodic table. They are strikingly associated to the great challenges for our future: these are water, sustainability, energy, open chemistry, the history and the educational perspectives of the periodic table.

During its long path of progress and civilisation mankind has strongly modified nature to make our planet more comfortable, but at present we must be very careful with some dramatic changes that are occurring in our Earth. Science and technology, and chemistry primarily, can help mankind to solve most of the environmental and energy problems that emerge, to build a radically different approach from that that has prevailed in the last two centuries. It is a fantastic challenge, since for the first time we can consider nature not as a system to simply exploit, but a perfect ally for improving life conditions in the whole planet. Chemistry has already engaged and won a similar challenge when, understanding the pollution problems generated by a chaotic and rapid development, succeeded in setting up a new branch, green chemistry, that turned upside down several research topics. Now is the time to develop sustainable chemistry: the occurring events demand that chemists propose new routes and innovative approaches. In the last two centuries we have transformed immense amounts of matter from nature into waste without thinking that we were using non renewable energy sources. We have been acting as our natural resources were unlimited, but knowing that they are instead limited. Now we are realizing that it is not possible to continue along this road. Our planet and our atmosphere are made of finite materials and their consumption during the last two centuries has been impressive. Some elements that are crucial for current and future industrial countries are known to be present on Earth crust in very small amounts and their recycling from waste cannot be a choice anymore, but it is rather an obligation.

Climate is another big problem associated to the terrific changes occurring in some equilibria, both as a consequence of the violent industrial development and energy consumption. We need, and we will always need more and more, an immense amount of energy. The only solution to secure wellness to future generations is the conversion to renewable energy sources. In this view, food and water, due to the strong increment in the demographic indices, could become the true emergencies for billions of individuals. Looking at the picture I tried to draw in this short preface it becomes more clear why we selected those topics for our special issues.

I am optimistic, and I have the strong confidence that chemistry, that studies matter and its transformations, will give mankind the picklock to overcome those challenges.

We will definitely need insightful minds, creativity, knowledge and wisdom.

Luigi Dei
President of the University of Florence

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Editorial

# Where Does Chemistry Go? From Mendeelev Table of Elements to the Big Data Era

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> *Who is each of us if not a combination of experiences, information, readings, imaginations? Every life is an encyclopedia, a library, an inventory of objects, a sample of styles, where everything can be continually re-mixed and rearranged in all possible ways " (from Italo Calvino, American Lessons, Six Memos for the Next Millennium, 1988)*

One hundred and fifty years ago the Russian chemist Dmitri Ivanovich Mendeleev published the first "Periodic System of the Elements" originated to display the periodic trends of the chemical elements known at that time and possibly to predict unknown elements supposed to fill the empty spaces, by predicting their properties. His prevision turned out to be essentially correct. He had about sixty elements in his periodic table of 1869. Other naturally occurring elements were discovered or isolated in the following years, and various further elements have also been produced synthetically. In his honor element 101, discovered in 1905, was named "**mendelevium**". The modern periodic table, of 118 elements now, constitutes an important framework for exploring chemical reactions; it provides the basis for the discovery or the synthesis of further new elements and for the development of new theoretical models. Although other chemists at the time of Mendeleev attempted to organize the known chemical elements in a system, the extraordinary and visionary intuition of Mendeleev was to use the trends in his periodic table to predict the properties of missing elements. The philosophy behind the Mendeleev conceptions about systemizing the extant knowledge of chemistry and possibility to predict the missing information, thanks to the network support, can be considered a pioneering approach of the new science called "Systems Chemistry" and the harbinger of the modern "Predictive Chemistry". Indeed, systems chemistry is defined as "the science which study the networks of interacting molecules, to create new functions from an ensemble of molecular components at different hierarchical levels with emergent properties" [1]. As in any systems science, systems chemistry too benefits of the massive outburst of big data.

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Big Data indicate data sets large and/or complex enough, that traditional processing and analysis are not sufficient. Now as then, in the Mendeleev's age, the need for rationalizing and systemizing data is compelling. Indeed, in the case of big data, one must deal with a large amount of data with the need of dimension reduction, as in the process of zipping them, to compress large quantity of data into smaller equivalent sets. Statistical/computational intelligence tools such as principal component analysis, fuzzy logic, neuro-computing, evolutionary computations etc. are developed to reduce the size of big data sets and extract valuable information. In this regard, we see the today-approach towards data-driven chemistry as an evolution of the Mendeleev philosophy, rather than a revolution. Dmitri Mendeleev was actually the first to envision the possibility to systemize chemical knowledges in a frame were much space would be available to the unknown elements which would fit within a "systemic" view of the system, and he was, therefore a real pioneer of the modern predictive data science able to extract knowledge or insights from large data sets. The figure of Dmitri Mendeleev has inspired much fascination and his story about the idea that he said to have had it envisioned in a dream is amazing: he dreamed all the elements falling into the right place. However, we think that his philosophical thoughts had not influenced and not reported enough by the historians of science. As confirmation of this idea is the fact that Mendeleev never got the Nobel Prize although candidate several times: in 1901, 1905 and 1906, but he lost because, according to the committee, his work was already too old and well known: paradoxically, the Mendeleev's table was victim of its own success. In 1906 the Nobel award went instead to Henry Moisson for the discovery of fluorine, an element that was right were the table predicted to be.

The following year Mendeleev died, and so his table of the elements could not boast a Nobel. However, we think that with the advent of Systems Chemistry, Mendeleev's philosophy of logic systematization and prediction of missing elements is taking a rematch. Being the focus of systems chemistry research on the overall network of interacting molecules and on their emergent properties, the way in which specific interactions between the components propagate through the system may predict these emergent properties. The term "systems chemistry" was first used in 2005 by Von Kierowski[2]. He stated that: "combining kinetic, structural, and computational studies on complex dynamic feedback systems may lead to the field of systems chemistry". The approach is exemplified by the analysis of a simple organic self-replicating system that has the potential to express both homochiral autocatalysis and heterochiral cross-catalysis. Von Kiedrowski claimed that this new approach could pave the way to a new field he named "systems chemistry", that is to say, the design of prespecified dynamic behavior. Later on, this proposal moved away from its reductionist approach to the study of multiple variables simultaneously [3,4,5]. Several topics related to systems chemistry bring also philosopher and existential questions such as: what made possible on the prebiotic Earth the "transmutation" of a complex mixture of molecules into living chemical systems?; why the biochemical building blocks of life were selected and how some of these biomolecules developed to have specific chirality? The latter poses fundamental questions about the origin of chiral asymmetry in biological molecules which still remains without answer[6,7]. Systems chemistry attempts to address these issues by creating synthetic systems models with properties that could reflect aspects of prebiotic biogenesis. Another topic at the core of systems chemistry is the quest for de novo life.

However, systems chemistry encompasses much more than these issues and put forward a plethora of new opportunities for the discovery of dynamic figures in all areas in chemistry. In 2005 in Venice during a conference an early consensus definition of systems chemistry was established as below[8]:

- A conjunction of supramolecular and prebiotic chemistry with theoretical biology and complex systems research addressing problems relating to the origins and synthesis of life.
- The bottom-up pendant of systems biology towards synthetic biology.
- Searching for a deeper understanding of structural and dynamic prerequisites leading to chemical self-replication and self-reproduction.
- The quest for the coupling of autocatalytic systems, the integration of metabolic, genetic, and membrane-forming subsystems into protocellular entities.
- The quest for the roots of Darwinian evolvability in chemical systems.
- The quest for chiral symmetry breaking and asymmetric autocatalysis in such systems.

Since then, systems chemistry has had a big boost due to the advent of data science tools.

Data science is defined as a multi-disciplinary science that uses scientific methods, processes, algorithms and systems to extract knowledge and insights from structured and unstructured data[9]. It has been presented as the fourth pillar of science (being theory, experimentation and simulation the other three). With the advent

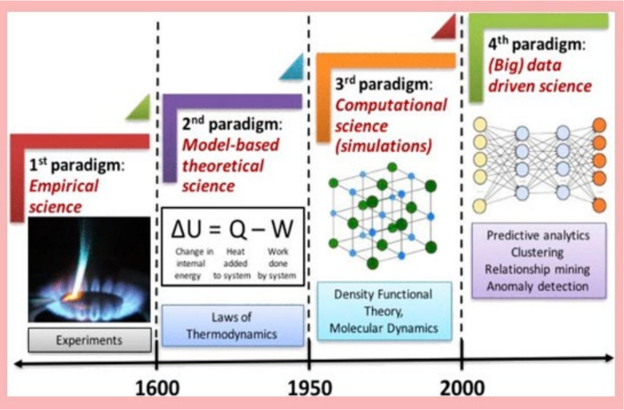

**Figure.** The four paradigms of science: empirical, theoretical, computational, and data-driven. Image from Agrawal and Choudhary [10].

of "omics" in life sciences (genomics, proteomics, transcriptomics, metabolomics etc.) and the advent of modern high-throughput techniques of analytical chemistry and molecular biology we are able to produce a huge amount of data. Thus, the way we undertake research is presently changed and the data drive science is considered the fourth paradigm (see Figure). The increasing rate of data generation in all scientific disciplines is providing incredible opportunities for data-driven research, transforming our current processes. The exploitation of so-called 'big data' will enable us to undertake research projects never possible before but also stimulate us to re-evaluate our previous data.

The 2002 was identified as a turning point in data and a landmark year when digital took over from analog. Indeed, it was observed that in 2009, more data worldwide were produced than all the preceding years put together. The advent of the big data age changed irreversibly the paradigm of science. Thousand year ago, science was empirical, based on, or confirmed by observation rather than theory or logic speculations. A few hundred years ago science was based on theoretical models. A few decades ago, when computer modeling simulation was introduced to understand complex phenomena, the paradigm of science changed again. Today we are witnessing the coming of the fourth paradigm of science which unifies theory, experiments, simulation, computation, creating big data sets and entering the era of "Data Science" or "Systems Sciences", originating the fourth paradigm of science which is data-driven discovery. The possibility of collecting big data has surpassed, by far, the present capability of analyzing them. At this purpose more and more dedicated, open-source "high-performance computing platforms" are being developed. Open-access data repositories, where multiple databases or files or experimental results are loaded by scientists, are the backbone of these platforms and stimulate a collaborative attitude among scientists.

Unfortunately, data science approach represents still a rather unexplored field among the community of chemical scientists, thus, limiting many opportunities for advancing chemical sciences. Conversely, many advances are being put in place in the systems biology area and learning from biological complexity can be a way of stimulating new chemistry. Biological systems display an incredibly large amount of amazing capabilities that can be a rich source of models for new areas of chemistry to design nonbiological systems. It is a big challenge for the chemistry of the 21st century, perhaps it is the challenge.

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# Visualizing Solubilization by a Realistic Particle Model in Chemistry Education

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**Abstract**. An application for the visualization of the mixing process of two different types of structureless interacting particles is presented. The application allows to demonstrate on a qualitative basis, as well as by quantitatively monitoring the time evolution of the fractions of aggregates of different sizes, that the formation of a homogeneous mixture is the result of favorable solute-solvent interactions as well as by temperature. It is suggested that, along with the use of suitable macroscopic examples, visualizations by the present application are useful in elucidating concepts related to miscibility/solubility. The application is based on a two-dimensional realistic dynamic model where atoms move because of their thermal and interaction potential energies and their trajectories are determined by solving numerically Newton's laws according to a Molecular Dynamics (MD) scheme. For this purpose, a web-based MD engine was adapted as needed. It is suggested that, when possible, using a realistic simulation rather than simple animations offers several advantages in the visualization of processes of interest in chemistry education. First of all, in a simulation the outcome of the process under study is not set *a priori* but it is the result of the dynamic evolution of the system; furthermore, specific parameters can be systematically varied and the effects of these changes can be investigated. The application can be used at different levels of detail and in different instruction levels. Qualitative visual observations of the obtained mixtures are suitable at all levels of instruction. Systematic investigations on the effect of changes in temperature and interaction parameters, suitable for senior high school and college courses, are also reported.

**Keywords**. Chemistry Education, Intermolecular Interaction, Mixtures, Molecular Dynamics, Particle Model, Solubility.

## INTRODUCTION

The particle model of matter has been extensively used in the past to interpret and visualize different kinds of chemistry processes and phenomena for education purposes also pointing out its shortcomings as a potential source of misconceptions.[1-15]

An effective way of introducing the particle model of matter, in our opinion, is to quote a quite famous sentence[16] by Richard Feynman (1918-1988), Nobel laureate in physics in 1965:

*If, in some cataclysm, all of scientific knowledge were to be destroyed, and only one sentence passed on to the next generations of creatures, what statement would contain the most information in the fewest words? I believe it is the atomic hypothesis (or the atomic fact, or whatever you wish to call it) that all things are made of atoms—little particles that move around in perpetual motion, attracting each other when they are a little distance apart, but repelling upon being squeezed into one another. In that one sentence, you will see, there is an enormous amount of information about the world, if just a little imagination and thinking are applied.*

The above sentence suggests that the main ingredients to be stressed and clarified are: existence of discrete particles, motion and interactions. These concepts are equally important and they must be all present in any exhaustive implementation of the particle model for education purposes but they should be introduced gradually in a process of progressive development of the model inspired by the comparison between its predictions and experimental evidences.

In particular, when only still pictures are used, the dynamic properties of matter are inevitably lost in spite of the fact that they are as important as structural considerations in determining the system overall behavior. This is important for physical properties, where no changes in chemical identity of the particles are involved, as well as for chemical transformations.

Due to the continuing progress in computing power and in modelling software, in addition to advanced tools for the visualization of molecular structures, many different dynamic visualization tools have become readily available, either on the web or stand-alone, even for popular devices such as tablets and smartphones.[17-23]

However, in most animations,[22, 24-29] particle motion is defined in a more or less arbitrary way. Realistic dynamic models are seldom used for education purposes.[30-35] A computer application for the visualization of the aggregation and growth process of nanoparticles by a Molecular Dynamics (MD) realistic model has been recently presented.[36] In the same study, the advantages of adopting, when possible, a molecular simulation perspective rather than using simple animations have been discussed.

In this work, we preset an application, based on the same realistic model, designed to introduce a progressive development of the particle model for visualization and education objectives. The application was specifically implemented for elucidating solubility, i.e. the phase behavior of a two-components mixture of different particles. After a brief summary of the Molecular Dynamics (MD) method, the application is discussed by following a step-by-step sequence leading to its final objective.

## THE MOLECULAR DYNAMICS METHOD

In the MD simulation method, a fixed number of atoms/molecules move in a given volume and behave as classical objects. Their motion is the consequence of both thermal and interaction potential energies. The particle motion is ruled by Newton's classical laws:

$$m_i\ddot{\boldsymbol{r}}_i = -\nabla_i(\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots\ldots, \boldsymbol{r}_N) \quad (1)$$

where $\mathbf{r}_i$ is the position vector of the i-th atom and $m_i$ is its mass. Hence, in order to calculate the trajectory of each atom, one needs to solve numerically 3 second order differential equations for each time step *d*t. As a consequence, for the design of an MD simulation, substantial computing and programming abilities are required. However, as already pointed out[36] and as done in the present work, an efficient and easy to use web-based resource[37] can be used.

The interested reader can find full details about MD elsewhere.[31, 38-40] In what follows, we will limit the discussion to the dynamic description of a set of N interacting structureless atoms.

In the case under consideration, an appropriate form of the interaction energy is given by the so-called Lennard-Jones (LJ) potential:

$$\boldsymbol{U}_{i,j,\ i\neq j} = 4\boldsymbol{\varepsilon}\bullet\left[\left(\frac{\boldsymbol{\sigma}}{\boldsymbol{R}_{ij}}\right)^{12} - \left(\frac{\boldsymbol{\sigma}}{\boldsymbol{R}_{ij}}\right)^{6}\right] \quad (2)$$

$$\boldsymbol{U} = \frac{1}{2}\bullet\sum_{i,j,\ i\neq j}\boldsymbol{U}_{i,j} \quad (3)$$

where $R_{ij}$ is the distance between the i-th and j-th atom, ε is a parameter related to the attractive strength and σ is the atomic diameter corresponding to the contact distance. As a consequence, the total potential energy is calculated as the sum of all pairwise contributions defined by Equation 2. In this equation, the first term, sharply increasing with decreasing interparticle distance, is attributable to repulsions at contact distances whereas the negative term represents long-range attractions.

In order to start an MD simulation, one has to define initial positions and velocities of each particle. A common choice is to place the N particles in random positions of the simulation cell with a velocity distribution close to that given by the Maxwell-Boltzmann particle distribution[41]:

$$f\left(v\right) = 4\pi\left(\frac{m_i}{2\pi k_B T}\right)^{3/2} v_i^2 exp\left(-\frac{m_i v_i^2}{2k_B T}\right) \quad (4)$$

where *f* (v) is the probability distribution of speed, $m_i$ and $v_i$ are the mass and the component of the velocity of the i-th atom, T is the temperature, $k_B$ is Boltzmann's constant.

The MD procedure consists in solving Equation 1 for each atom at a given time step and iterating for successive discrete time steps, thereby producing a time sequence of configurations.

## PARTICLE MODEL IMPLEMENTATION

In this work, we present a computer application[42] which uses Molecular Workbench (MW), an open-access web-based general purpose MD engine developed by the Concord Consortium.[37] This Java based platform provides 2D and 3D classical molecular dynamics engines. In addition to ready-made examples, the user can design and customize new models or activities. Full details about the computation environment are given elsewhere.[35]

In the use of the application, the first step is to illustrate the opening sentence in Feynman's statement mentioned in the Introduction: *things are made of atoms—little particles that move around in perpetual motion.*

When the application is first started, at the top of the page, the user is presented with an empty container: a 100 x 100 x 100 $Å^3$ cell. An arbitrary number N ($0 \leq N \leq 500$) of identical monoatomic structureless particles with diameter $\sigma = 2.0$ Å and mass m = 20 $gmol^{-1}$, can be placed in random positions of the simulation cell by clicking on the appropriate control after selecting the desired number of particles. It is important to specify that these particles behave as tiny hard spheres and, as a consequence, their shape and size cannot change. After selecting the desired value of the temperature ($100 \leq T \leq 1000$), by clicking on the "Run the model" button, the simulation will start and the particles will move by following Newton's laws of motion and undergoing virtually elastic collisions among them. In this case, no long-range attractive interactions were set, i.e. the $\varepsilon$ value in Equation 2 was set to a very small value ($\varepsilon = 0.01$ eV). As a consequence, it can be easily observed that, between collisions, particle motion is unaffected by the presence of the other particles. Students should be encouraged to observe and describe the behavior of the system and, if desired, the instructor may ask appropriate questions in order to assess students' understanding. For example, in lower secondary school classes, students might be asked to suggest the nature of the medium in which the particles are moving or whether there might be a tangible consequence of the particle collisions on the container walls. At this stage, other possible qualitative observations that the instructor might consider to initiate, deal with the effect of changing the temperature on particles velocities and/or that of changing the number of particles in the given (fixed) volume on the empty space available to the particles. This latter concept is connected to those of compressibility and density of gases. The instructor will decide the level of the discussion based on the students' background. It is important to stress that, in this preliminary phase, students should be mainly asked to observe the phenomena on their own and address possible problematic situations appropriately proposed by the instructor.

From now on, all further demonstrations by the current application will be implemented in a 2D environment. This choice is justified by the fact that the application should be run interactively and students should be put in the position to observe significant results in a reasonable time. In an MD simulation, the most time-consuming step is the double loop (see Equation 3) in which the interactions between each particle and its neighbors are calculated. The number of terms to be calculated scales roughly as $N^2$. As a consequence, computing time increases quadratically with N. For this reason, it is important to keep the number of atoms N as small as possible. By adopting a 2D environment, it is possible to reduce drastically the number of particles to be included in the simulation without any significant loss in physical realism, at least for the phenomena and concepts here considered.

In the application, the second demonstration, at the bottom of the page, is designed to study in more detail a few of the concepts already introduced. In particular, in addition to their number, the size and mass of the atoms can be changed within specified ranges. Different particle colors are used when their mass is changed, in order to indicate that the type of particles has changed. At this point, a definition of *substance* at the submicroscopic level can be introduced as a portion of matter constituted by identical particles. Particles of a given substance, then, are identical but they are different from those of a different substance. Thus, a mixture of different substances contains particles of different types. It might be objected that a mass change without a corresponding change in atomic size is unlikely. However, at this stage, it was chosen not to stress the correspondence between atomic properties and their chemical identity. In our opinion, this correspondence will come into play later when elements and periodicity will be introduced.

Once again, in introductory science/chemistry instruction (upper primary and lower secondary school classes), effects due to changes in atomic properties (size and mass) and temperature can be investigated on a qualitative basis. In upper high school and introductory university courses, a more quantitative

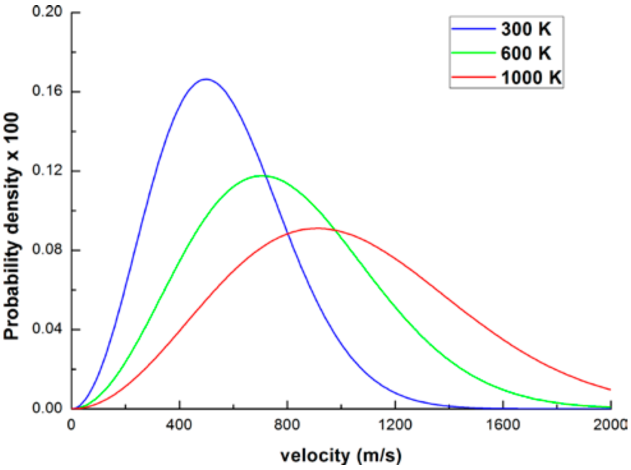

**Figure 1.** Maxwell-Boltzmann probability distribution of atomic velocities (see Eq. 4) at the temperatures specified in the legend for a set of 200 atoms of mass m = 20 g/mol. The MD time step was 1 fs.

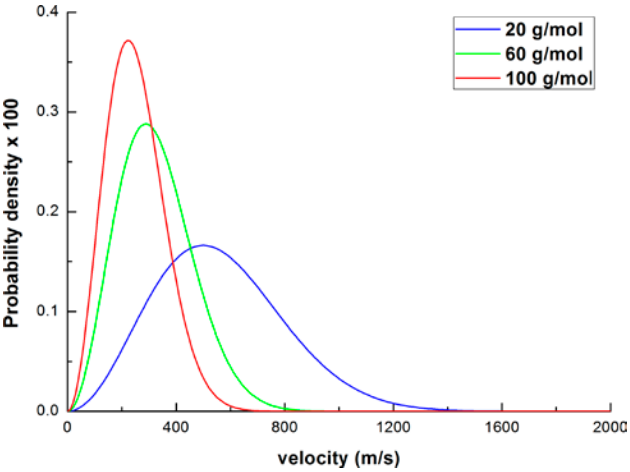

**Figure 2.** Maxwell-Boltzmann probability distribution of atomic velocities (see Eq. 4) at T = 300 K for a set of 200 atoms with mass m specified in the legend. The MD time step was 1 fs.

approach can be adopted. In this part of the application, it is possible, for example, to calculate the Maxwell-Boltzmann (see Equation 4) speed and velocity distributions. It might be recalled that the difference between the two functions is that, in the former case, one considers a scalar quantity, i.e. the module of the velocity vector.

In Figures 1 and 2, results obtained with the specified parameters demonstrate that the most probable atomic speed increases with increasing temperature and decreasing atomic mass. This evidence illustrates the connection between temperature and the average kinetic energy of the atoms. The instructor will be able to tune the level of this description to the students' background even recalling basic concepts about the laws of motion as needed.

The corresponding velocity distribution function that can be calculated by activating the appropriate button in the application, will exhibit a maximum at $v \approx 0$ indicating that, since atoms are moving in all directions, there is no net resulting component of the velocity vector.

At this point of the teaching sequence, interactions among particles can be introduced. Going back to Feynman's quote:

> *…attracting each other when they are a little distance apart, but repelling upon being squeezed into one another.*

Therefore, the interaction energy is negative (attractive) when atoms are at intermediate distances and it becomes positive (repulsive) when they get close to each other. When interatomic average distances are large, the interaction potential approaches zero. For the case under consideration here, a convenient form of the interaction potential is that given by Equation 2.

The introduction of interactions and the balance with atomic average kinetic energy leads to discussions related to physical states of matter, in particular the existence of condensed (solid and liquid) phases and phase transformations. This topic is not part of the present work and it will not be discussed further. However, many different dynamic applications can be found in the literature. In particular, an explicit connection between interactions, particle motion and phase behavior is available in a recent study[36] as well as ready-made examples in the MW website.[43, 44]

## MIXTURES AND SOLUBILITY

The concept of solubility is one of the most common themes in chemistry and, at the same time one of the most difficult to grasp by students on a conceptual basis. Anyone is familiar with the macroscopic difference between a solution, such as the result of the addition of a not too large amount of sodium chloride to water, and the result obtained by mixing olive oil and water. However, things get complicated when rigorous definitions are sought. These definitions, on the macroscopic level, essentially involve the concept of *phase* and, thus, a homogeneous mixture (a solution), consists of a single phase whereas, in a heterogeneous mixture, at least to different phases can be detected. On the submicroscopic scale, in spite of its potential conceptual hurdles, the particle model offers, in our opinion, a more logical representation, particularly when the dynamics are also taken into account. In this perspective, in a mixture of particles of type A and type B, a phase is recognizable as a cluster of B particles dispersed within A particles. Incidentally, a system containing different phases of the same substance, such as ice floating in liquid water, can be described as clusters of particles of a given type in a given structure within particles of the same type in a different structure.

The factors affecting the stability of a mixture of two different substances and determining solubility/miscibility can be rationalized by analyzing the thermodynamics of the mixing process.[45,46] This topic has been also the object of many studies for education purposes.[47-52] In short, entropy always favors mixing whereas reciprocal particle interactions between like and unlike species can influence the process in both directions. In addition, temperature plays a role in that, in most cases, the mixing of simple systems is favored by an increase in the temperature.

All the above ideas have been gathered in the second page of the present application. This page also contains a link to a brief section on general background concepts. When the application is first started, the user is presented with an empty container: a 60 x 60 Å$^2$ cell. A barrier divides the cell into two compartments where a specified number of equally sized (σ = 1.4 Å) A (blue) and B (green) particles of the same mass (m = 40 gmol$^{-1}$) can be placed. The user selects the total number of atoms N ($50 \leq N \leq 200$) and the fraction (0-0.5) of B atoms. When this is done, the specified number of B atoms is placed, in random positions, on the left hand side of the barrier; the number of A atoms, resulting from the specified B fraction, is placed, in random positions, on the right hand side of the barrier. In Figure 3, a typical configuration of a sample simulation with the specified parameters is shown.

Furthermore, the strength, ε (eV) of the attractive part of the LJ potential (see Equation 2) between all particles will have to be set. The user can set independently the strength of the potential between A particles ($\varepsilon_{A\text{-}A}$), between B particles ($\varepsilon_{B\text{-}B}$) and between A and B particles ($\varepsilon_{A\text{-}B}$). Finally, a specific control allows to set the temperature T of the simulation. When all parameters have been selected, the simulation will start by clicking on the "Run the model" button. By clicking on the "Mix" button, the gate between the two compartments opens and the two groups of particles mix.

During the simulation, the plot on the right will display the time evolution of the fractions, with respect to the total number of B particles present as B monomers, B pairs and B atoms present in larger aggregates. In this plot, the red line, initially set at a value of 1, drops to 0 when the gate is opened.

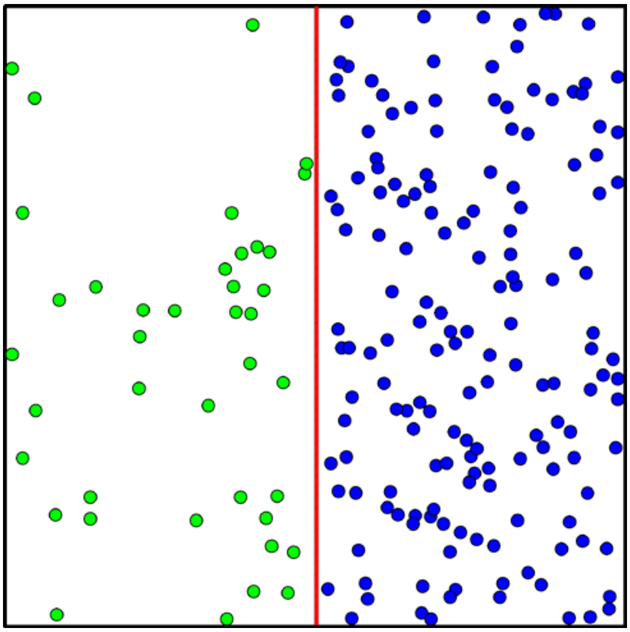

**Figure 3.** Initial configuration of a mixture of A (blue) and B (green) structureless equally sized (σ = 1.4 Å) particles in a 60x60 Å$^2$ simulation cell. The total number N of particles was 200 and the fraction of B particles was 0.2. At the beginning of the simulation, A and B particles are contained in two compartments separated by the impermeable barrier also shown.

In Figure 4, results of a sample simulation performed with the specified parameters are shown. It can be seen that, when all interaction parameters are very small (ε ≈ 0 eV), the driving force to mixing is entropy and a homogeneous distribution of B particles in the A solvent is quickly obtained.

By running the simulation at different thermal conditions, it is easy to prove that temperature influences the rate of the mixing progress but not its outcome.

In Figure 5, results from a simulation performed with parameters favoring B-B interactions are shown. It can be seen that, after the barrier is removed, the substances mix but, because of preferential B-B interactions, the solute is present as aggregates of different sizes within the A matrix.

By prolonging the simulation, it can be observed that B clusters tend to merge with each other forming larger aggregates, thereby maximizing B-B contacts and minimizing energy. In this case, a heterogeneous mixture of B in A is obtained. The same qualitative conclusions are obtainable from the plot on the right of the same figure: a progressive decrease in the fraction of B monomers corresponds to an increase of the fraction of B aggregates.

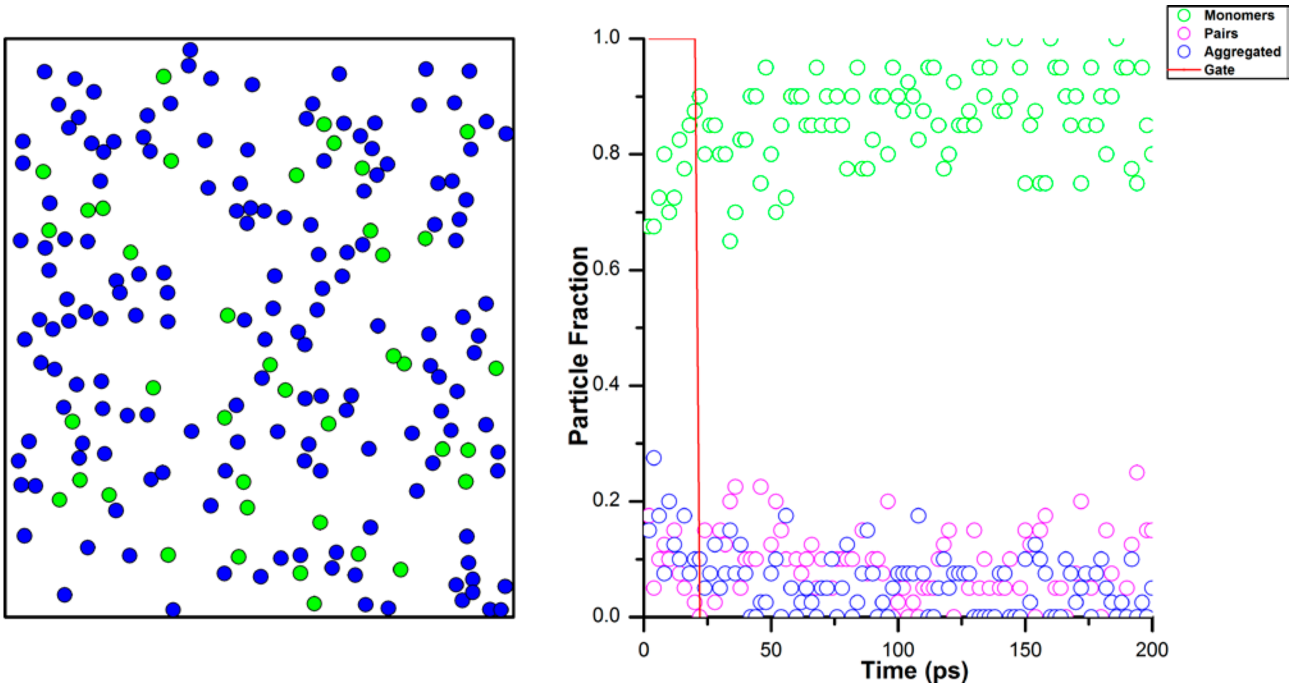

**Figure 4.** Left: snapshot of the configuration obtained after 200 ps of a simulation for the mixture described in Figure 3 at T = 300 K and no interactions between the particles. Right: time evolution of the fraction of B monomers, pairs of B atoms and total aggregated B atoms present in clusters of more than 2 B atoms for the same simulation. The time at which the red line sharply drops to zero indicates when the gate shown in Figure 3 was opened and the particles were allowed to mix. The MD time step was 1 fs.

On the contrary, as shown in Figure 6, by adopting conditions favoring A-B interactions a homogeneous dispersion of B in A is quickly obtained. The plot on the right demonstrates that the vast majority of B atoms is present as monomers; a few pairs and slightly larger aggregates are also present.

The effect of temperature is demonstrated in Figure 7. In this case, the heterogeneous mixture obtained under the conditions of Figure 6, was heated to two different temperatures. Heating favors the formation of a homogeneous system as shown by the progressive "melting" of the B aggregates.

This conclusion is supported by the plot on the right showing a progressive increase in the fraction of B monomers at the expense of large B aggregates.

As an additional evidence in support of the previous conclusion, in Figure 8 results obtained at T = 500 K from a simulation started from an initial configuration similar to that of Figure 3 are shown. At this temperature, contrary to what observed at T = 300 K (see Figure 5), a homogeneous B in A mixture is obtained.

In the plot on the right, it is demonstrated on a quantitative basis that, throughout the simulation, the vast majority of B atoms is present as monomers.

## DISCUSSION

The present application has been designed to introduce the basic concepts of the particle model of matter and, in particular, its dynamic properties. It has been pointed out elsewhere[36] that using a realistic model for describing the motion of atoms and molecules, rather than using animations based on more or less arbitrary successions of still pictures, carries important advantages from an education viewpoint. The most relevant advantage is that the phenomenon under study is not a preconceived idea but, rather, it is the result of the physical laws ruling the behavior of the system. With this in mind, as explained above, the application was designed as a realistic MD simulation in which simple structureless monoatomic particles move according to Newtown's laws of motion. After a preliminary step, aimed at familiarizing the students with the behavior of a system of non-interacting particles, a realistic interaction potential (see Equation 2) was introduced and attention was mainly focused on the properties of mixtures.

Concepts related to solubility and the processes determining the formation of homogeneous or heterogeneous mixtures are very important in chemistry and, at the same time, they are among the most dif-

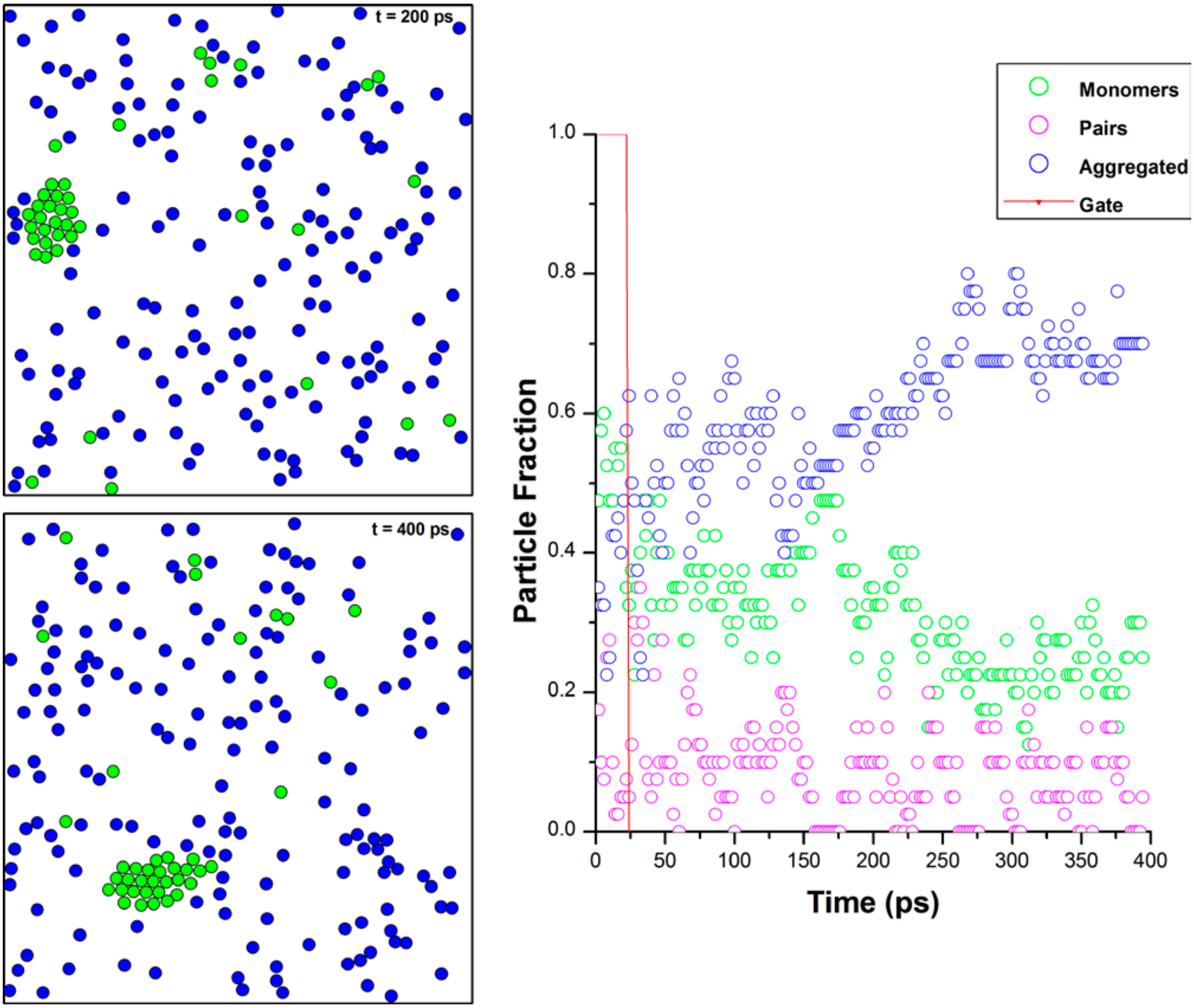

**Figure 5.** Left: snapshots of the configurations obtained after 200 ps (top) and after 400 ps (bottom) of a simulation for the mixture described in Figure 3 at T = 300 K. The interaction parameters (eV) were: $\varepsilon_{A\text{-}A} = 0.01$, $\varepsilon_{B\text{-}B} = 0.1$ and $\varepsilon_{A\text{-}B} = 0.05$. Right: time evolution of the fraction of B monomers, pairs of B atoms and total aggregated B atoms present in clusters of more than 2 B atoms for the same simulation. The time at which the red line sharply drops to zero indicates when the gate shown in Figure 3 was opened and the particles were allowed to mix. The MD time step was 1 fs.

ficult to grasp by the students. A simplified representation, as that adopted in the present work, might be useful because it attributes to different interactions between solute and solvent particles the origin of the dissolution process.

Since the adopted model is based on explicit physical laws, it is possible to change specific parameters and observe the effects of these changes on the phenomenon under investigation. In the case under consideration, i.e. the mixing process of particles of different types, in addition to parameters defining the identity of the particles (size and mass), the relevant variables are temperature and attractive straight parameters. As a consequence, the application was designed to focus on the latter.

Results reported in Figure 4 demonstrate on a qualitative basis, that, when no interactions are present, two different substances will mix at any temperature because there is no reason for particles of one type to favor regions reach of particles of the same type. This idea is a qualitative way of describing the spontaneous process which, from a state consisting of two separate A and B substances, leads to a homogeneous A-B mixture, with a corresponding entropy increase; the instructor will be

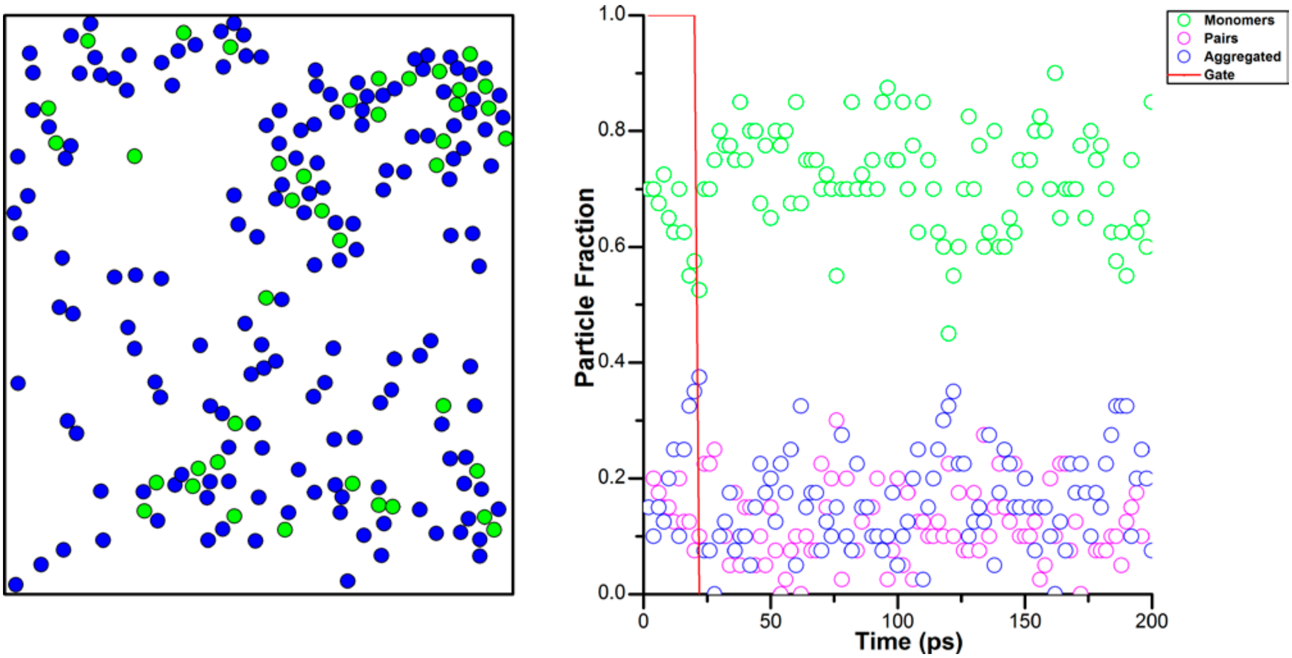

**Figure 6.** Left: snapshot of the configuration obtained after 200 ps of a simulation for the mixture described in Figure 3 at T = 300 K. The interaction parameters (eV) were: $\varepsilon_{A\text{-}A} = 0.01$, $\varepsilon_{B\text{-}B} = 0.05$ and $\varepsilon_{A\text{-}B} = 0.1$. Right: time evolution of the fraction of B monomers, pairs of B atoms and total aggregated B atoms present in clusters of more than 2 B atoms for the same simulation. The time at which the red line sharply drops to zero indicates when the gate shown in Figure 3 was opened and the particles were allowed to mix. The MD time step was 1 fs.

able to calibrate the discussion also based on the school level. For high school students, the previous simple explanation will be sufficient, whereas in general chemistry university courses, more detailed references to thermodynamics laws can be made.

The results reported in Figures 5 and 6 demonstrate the effect of introducing preferential interaction energies between all particle pairs on the resulting mixture. When attractions between solute particles are stronger than those between solute and solvent particles, a heterogeneous mixture will originate in which aggregates of solute particles (a separate phase) are present in a matrix of solvent particles. On the contrary (see Figure 6), when attractions between solute and solvent particles are stronger than those between solute particles, a homogeneous system, i.e. a uniform distribution of solute particles in the matrix of solvent particles, is produced. It is important to underline that, in the two cases just described, the temperature is the same. In other words, the balance between kinetic and potential energies is unchanged. In secondary school chemistry instruction, where very limited thermodynamics concepts are present, the above discussion can be based on considerations similar to those used for explaining transformations of the physical state of a pure substance. Particles (different or alike) attract each other and, as a consequence, they tend to “stick”. At the same time, thermal motion, which is related to the temperature, pushes them apart. Therefore, temperature plays against aggregation and the net result of the competition between these two energy contributions, for a given substance and at a fixed temperature, determines the stable state of the system. Low temperatures favor aggregation and so do large interparticle attractions.

The above discussion is further supported by the results reported in Figure 7, where the temperature was raised and the consequent dissolution of the aggregates, formed at a lower temperature, was obtained. Raising the temperature had the effect of shifting the balance between kinetic and potential energies in favor of the former. The same conclusion can be reached by inspection of the results reported in Figure 8. In this case, the energy balance was in favor of the kinetic term from the beginning of the simulation and, as a consequence, no B-B aggregation was observed.

In summary, in our opinion, the application here presented offers the opportunity of letting the students observe, in an interactive fashion, the basic submicroscopic details underlying a mixing process. It is possible to use the application at different school levels: from the simple qualitative observation of the dynamic configurations, suitable for secondary school classes, to gradually

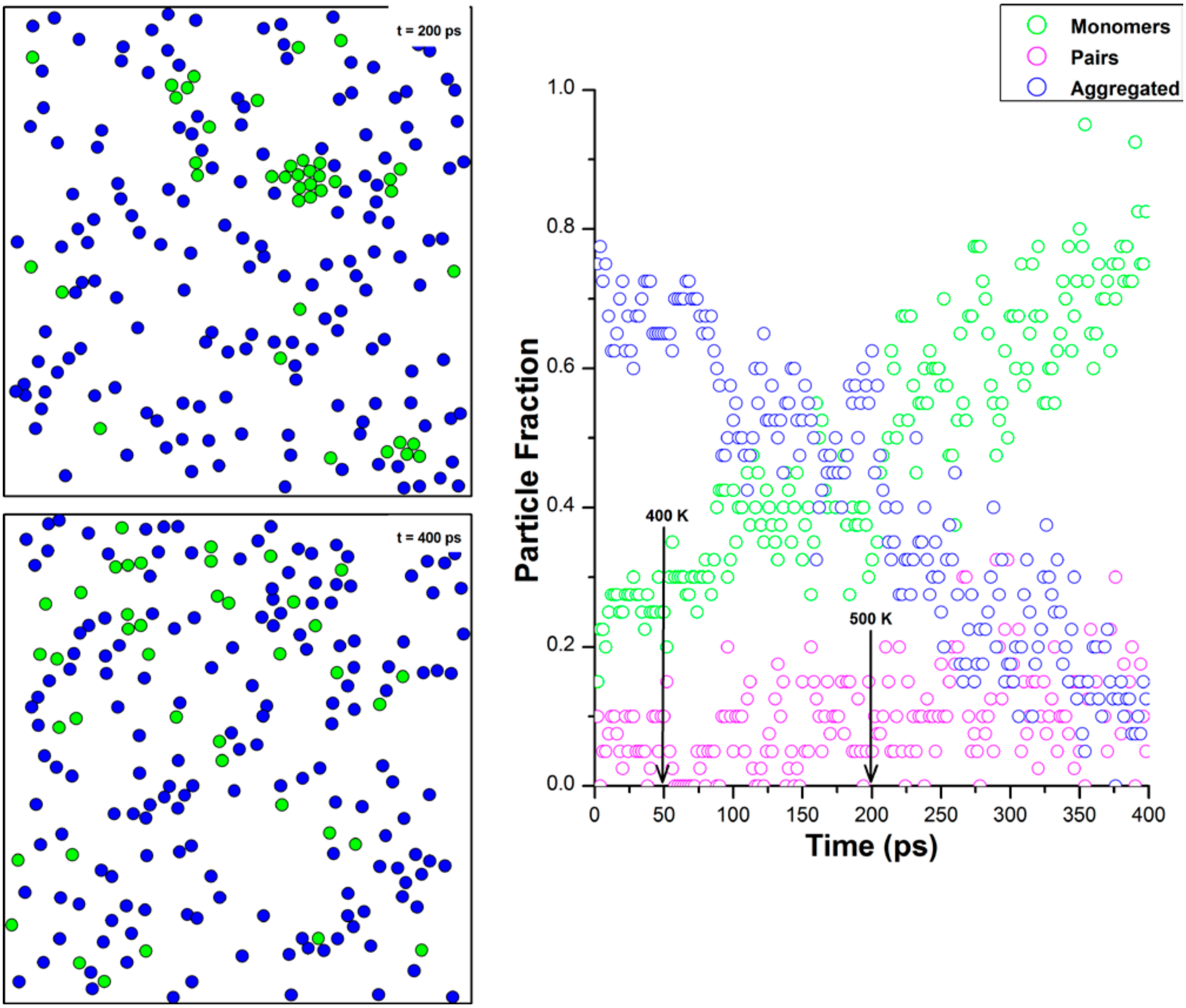

**Figure 7.** Left: snapshots of the configurations obtained after 200 ps (top) and after 400 ps (bottom) of a simulation started from the configuration obtained after 400 ps at the conditions of Figure 5. The mixture was heated at T = 400 K (top) and T = 500 K (bottom). The interaction parameters (eV) were: $\varepsilon_{A\text{-}A} = 0.01$, $\varepsilon_{B\text{-}B} = 0.1$ and $\varepsilon_{A\text{-}B} = 0.05$. Right: time evolution of the fraction of B monomers, pairs of B atoms and total aggregated B atoms present in clusters of more than 2 B atoms for the same simulation. The two arrows indicate the times when the temperature of the simulation was set to the specified values. The MD time step was 1 fs.

more detailed semi-quantitative analysis, also making use of the time evolution of the fractions of the different aggregated species present in the mixture, more appropriate for college general chemistry courses.

In any case, students should be made aware that the observed dynamics are the result of a physically sound model. Actually, in most cases, dynamic illustrations of the sub-macroscopic world generated by animations might be indistinguishable from those produced by a realistic simulation. However, students should be made aware of the difference.

Furthermore, the Java based MD engine[37] here adopted makes it possible to modify and adapt the existing code to special situations and, as a consequence, it is possible to let students' design computer experiments in introductory computational chemistry courses.

Needless to say, the physical description, despite its realistic nature, is very simplified. We propose that adopting a 2D representation does not introduce serious limitations as far as the physical reliability of the model is concerned. However, the very simplified nature of the interaction potential and, for example, the absence

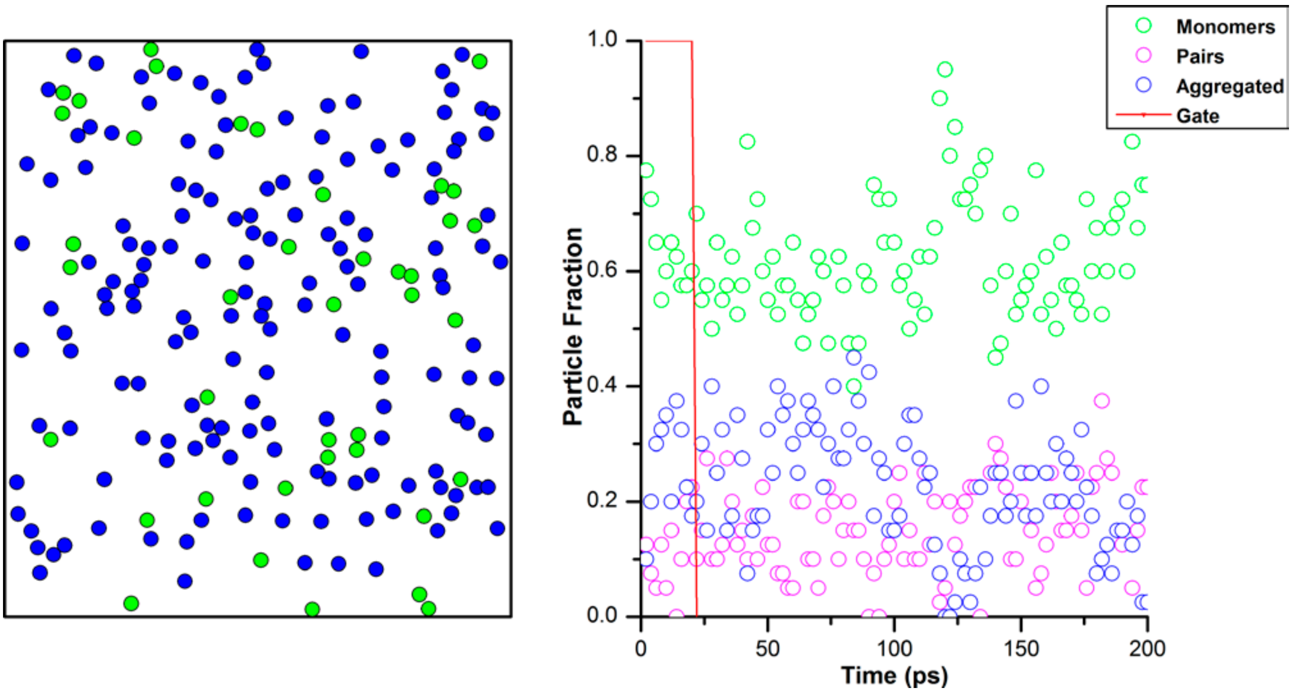

**Figure 8.** Left: snapshot of the configuration obtained after 200 ps of a simulation started from the configuration shown in Figure 3 at T = 500 K. The interaction parameters (eV) were: $\varepsilon_{A\text{-}A} = 0.01$, $\varepsilon_{B\text{-}B} = 0.1$ and $\varepsilon_{A\text{-}B} = 0.05$. Right: time evolution of the fraction of B monomers, pairs of B atoms and total aggregated B atoms present in clusters of more than 2 B atoms for the same simulation. The time at which the red line sharply drops to zero indicates when the gate shown in Figure 3 was opened and the particles were allowed to mix. The MD time step was 1 fs.

of specific interactions among solvent particles, is not suitable for representing special circumstances, such as aqueous solutions, where changes in solvent structure due to the presence of the solute are crucial. It might be recalled, for example, that these structural rearrangements might also lead to a temperature effect on solubility opposite to that predicted by the present model. Nevertheless, such complications might be considered as second order effects with respect to the basic ideas here developed.

## CONCLUSION

The particle model of matter is a powerful tool for describing the structure and the dynamic properties of matter at the submicroscopic level. With the present application, in our opinion, it is possible to demonstrate in a quite effective way that the study of the dynamic behavior is very often crucial in the understanding of fundamental concepts in chemistry. The adoption of a realistic model, based on classical Newtown's laws of motion, rather than using arbitrary animations, offers the added advantage of producing a physically meaningful picture as the outcome of the application of these laws rather than as a known *a priori* result. As a consequence, system parameters can be freely varied and the effects of these changes on the outcome of the simulation can be systematically investigated.

Depending on the students' background and degree of interest, the instructor will be able to calibrate observations and the subsequent discussion as needed. Even if students are not fully familiar with classical Newton's laws of motion, appropriate qualitative analogies based on common life situations, such as the motion of macroscopic bodies, could be used to clarify these concepts. In more advanced instruction levels, such as introductory general chemistry university courses, students are certainly acquainted with the physics concepts and basic math tools needed for making full use of the application.

Finally, it is worth mentioning that the present model and application is particularly suitable for the study of physical transformation of matter. The structureless nature of the particles rules out the possibility of changes in their chemical identity. Chemical transformations require more refined models.

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# Chemistry as Building Block for a New Knowledge and Participation

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**Abstract**. Chemistry has been identified as the central science: it connects the life sciences with the applied ones. In addition, the degree of branching around chemistry also influences social sciences and intersects in areas such as socio-economics and ethics. The knowledge of scientific concepts for non-specialized audiences, through communication and outreach activities, should be considered as a potent social heritage for humankind. An increase in awareness regarding the benefits based on science and trust would advantage the entire society. Herein, the relevance of a novel way to communicate scientific achievements is described: themes like circular economy and sustainable development are tackled to understand the role of chemistry in developing an *ex-novo* culture of knowledge.

**Keywords**. dissemination, knowledge, participation.

The perception around chemistry is usually felt as though one is observing a black box. However, even if the content of this black box should not be negatively conceived, this black box called *chemistry* is often associated with threats and complexities. Of course, who perceives the black box as above written is not the only "guilty". The role of chemistry as the central science should not only be delivered by specialists, like those who have attended chemistry classes[1], in places such as a high-school or a university, but also through different platforms which are more informal such as blogs, radio, magazines. It is a consequence that everything is heard, seen, smelt, tasted, and touched, involves chemistry. The comprehension of chemistry at some basic level is necessary to understand the world around us. However, with respect to the negative perception of chemistry, a major issue is usually represented by the difficulty of non-scientists to recognize the chemistry in everyday life: food digestion, use of soaps and detergents, pharmaceutical drugs, cooking, etc. which only represents a small section portion of daily chemistry. However, the voyage along the comprehension of chemistry and chemistry-related affairs has deeper roots[2] dating back to the Greek theory of matter (Plato and Democritus, in particular) and the study of alchemy. Which in turn led to the initial steps for empirical understanding. During the latter part of the 19th and 20th centuries, following the birth of Mendeleev's periodic table of the elements and the firsts atomic theories, chemistry has been associated with enormous possibilities towards life enhancements through its industrial growth.[3] In particular, the large scale and mass production processes of petroleum refinement has delivered feedstocks for fuels, solvents, lubricants, synthetic fibers, plastics, fertilizers, etc. for many other productions. Although the rising of the chemistry within the industry, together with its implementation especially in the 21st century, has led to undiscussed advantages in terms of wellness and possibilities, and two key, but opposing, perspectives should be considered. On the one hand, the positive view is that it reflects the knowledge and products given by chemistry, with major efforts in the advances in well-being over the past centuries with the introduction of smart materials, new vaccines and drugs for incurable diseases, sensors for early diagnosis, and more. On the other, chemistry has inadvertently, but not solely, contributed to a variety of emerging global problems. In this current period, termed ´the Anthropocene Age´, obvious consequences due to human activities has burdened the environment in numerous ways, such as increase in pollution, influencing climate change and over-consumption of natural resources.[4] Unfortunately, it seems that the latter perspective is the most popular and negative connotations are often associated with the word "chemistry" as a consequence of its history. So much so, that it has led to non-chemists experiencing "chemophobia"[5]. However, the forgetfulness of the benefits derived from chemistry should be carefully considered. From a chemist point of view, this trend needs to be inverted. Chemistry should be considered as a partner instead of an enemy; the black box should be converted in a transparent and open box. And to do this, the role of both chemists and non-chemists is of fundamental importance to establish the role of chemistry as an added resource for a new knowledge.

## TASK FOR CHEMISTS

The role of specialists needs to be directed towards better comprehension of the matter by identifying and implementing novel solutions to moderate potential crises. In particular, given the current state of the global environment, more sustainable processes for "greener" developments should be prioritized. The central role of chemistry represents the basis for the green development in numerous ways. By adopting new designs and methodologies, many strategies can be focused on providing more greener routes including generation and storage of sustainable forms of energy (solar energy, fuel cells, carbon capture), development of environmentally neutral synthetic methodologies for obtaining safer chemical products, solvents and (bio)catalysts, ensuring the recycle of limited resources and natural products, and the development of accurate analytical methodologies that can allow for real-time and in-process monitoring of hazardous by-products. To this regard, Anastas and Warner introduced the 12 principles of green chemistry in their book "*Green Chemistry, Theory and Practice*" in 1998.[6] Although the principles were outlined with the aim for greener chemical practices, the vision of sustainability within the chemical industries are often perceived as an increase of the costs of production. Where, by following or adhering to these principles, it is projected to be associated with costs > US$ 50 billion by 2020 within the chemical industry.[7]

Along with its centrality, the ethics of chemistry and chemical practices are reflected in different systems including the biosphere, human/animal health, politics and economics. To this regard, it represents the added point towards the growing of responsibility as the code of conduct proposed by the Organization for Prevention of Chemical Warfare (OPCW): a "Hippocratic Oath" for chemists need to be observed and actively driven forward by the major chemistry bodies and rigorously practiced.[8] However, the ethical engagement of chemists needs to be applied even far from the laboratory bench.

A broad communication of scientific achievements represents a crucial tool for making chemistry less distant, less remote and less arcane to lay audience. When chemists write articles on their findings, these are published in specialized journals, and the use of (necessary) jargon make the approach to non-specialists less effective. The majority of chemists do not actively work on communicating their research in ways that are friendly to non-specialists: from a career point of view, both in research and industry, there are no reasons for most research to be broadly communicated, and it is often perceived as a loss of time.[9] In addition, scientists doing public speaking are often considered to have lost their way as to what is really important. Of course, chemistry is a complex and broad field, that cannot be communicated in its entirety, and great efforts are always requested to make the communication charming. To eradicate the "chemophobia" feeling, the role of chemists should be focused on the adoption of brand-new communication strategies. Nowadays, contemporary platforms such as social media, blogs and videos, open up to a plethora of possibilities for reducing the gap between scientific achievements and society.

## TASK FOR NON-CHEMISTS

One of the great challenges for chemists in the 21st century is convincing the general public about the importance of chemistry and transforming the common image of factories pumping out pollution into an concept that shows progress and sustainability at its core. The perfect strategy for communicating the beauty of chemistry, and science in general, has no value if the receiver is not ethically able to participate and understand the information. However, interfacing with specialists through the different existing platforms only represents a step towards the establishment of a new concept of knowledge based on the scientific evidence, rationality and sustainability. For instance, 2019 has been the 150th anniversary and international year of the periodic table of the elements, and great efforts have been devoted to highlight the presence and the role of each element in everyday life. Chemical societies, magazines, roundtables, and radio stations have emphasized many aspects of the periodic table, including its history, global trends and perspectives on science for sustainable development, and the social and economic impacts of this field.[10] Following the same concept, by understanding the role of chemistry and its related processes, the end-users display a major responsibility in decision-making for future (but also current) action regarding tremendous issues that are affecting society. In the current society of consumption, the management of waste represents the latest environmental emergency. In large, it is connected with the manufacturing, exploitation and disposal of products, where approximately 30% of all discarded plastic is not managed or recycled. This does not fit well with a society like ours that largely rely on scarce resources. In this scenario, the urgent need for a shift to a circular model of economy needs competences of chemists for introducing novel ideas of manufacture,[11] the participation of citizens and the close relationship between the parties, i.e. chemists and non-chemists.

Shifting from linear to circular and a regenerative approach represents a turning point for changing the people´s choices of consumption. Novel acquired knowledge for reprocessing of goods and materials are expected to impact social, economic, and environmental fields by generating new, energy efficient, and reducing resource consumption and waste production. Simple actions like the cleaning and repurposing of glass bottles represents a quick and fast way to reuse and recycle glass, for example. Moreover, waste such as organic and/or inorganic can represent the starting point for industries and energy production systems. These actions represent only few examples that are required from a consciously involved citizen: the decrease of water pollution, the reduction of $CO_2$ emission, and improvements of environment, climate and human health, are just a consequence of a responsible behavior.

## CONCLUSION

Nowadays, the word "chemistry" is still associated to something negative. Although, many chemical disasters will not ever be forgotten, chemistry should also be synonymous with progress. The role of chemistry as the central science, and chemists too, represents a current key for a novel sustainable development for preventing the continuous decline of resources. The other key is represented by the citizens, that are asked to ethically collaborate with specialists, through actions in the field of circular economy and recycling. To do so, chemists and non-chemists need to be connected through engagement activities, such as education, where comprehension and awareness of the masses are strictly dependent on these features.

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# Tissue Engineering Between Click Chemistry and Green Chemistry

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**Abstract.** Tissue engineering is a strategy to improve or replace biological tissues and organs approached by an engineering point of view, thus combining the principal elements of tissues/organs (i.e. cells, scaffolds and bioactive molecules), as rebuilding a machine starting from its components. The concept of tissues and organ generation/regeneration has always impassioned mankind, starting from ancient religious and myth accounts, encompassing the Vedic culture, the Bible books and the Greek myths. Nowadays, thanks to advances in biochemical, technical, and medical knowledge many progresses have been achieved in this field. Indeed, the recent successful efforts to create biomaterial scaffolds have attracted a great deal of interest. However, despite of the significant progress, the realization of clinical and commercial products is experiencing frustration and slowdowns and sustainable tissue engineering may not be fulfilled with present approaches. The recent philosophy of "click" chemistry, to generate or functionalize synthetic scaffolds to obtain more biocompatible materials, and the introduction of "green" chemistry, focused on minimizing the use of hazardous substances, will give a new twist to tissue engineering and will open new fascinating and promising utilization. In this review we highlight the contribution that both click and green chemistry may represent for the development of new technologies in tissue engineering. The concern for a more sustainable and inclusive technology is also addressed.

**Keywords.** Tissue engineering, click chemistry, green chemistry, biomaterial.

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## LIST OF ABBREVIATIONS

BMP: bone morphogenetic protein
CuAAC: copper-catalyzed alkyne-azyde cycloaddition
DA: Diels-Alder (reaction)
GFs: growth factors
GO: graphene oxide
HA: hyaluronic acid
HAP: hydroxyapatite
miRNA: micro-RNA
MSCs: mesenchymal stem cells
NPs: nanoparticles
PEG: polyethylene glycol
PDA: polydopamine
PTT: photo-thermal therapy
PUFAs: poly-unsatured fatty acids
SP-AAC: strain-promoted azide-alkyne cycloaddition
TE: tissue engineering
TNF: tumour necrosis factor

## 1. INTRODUCTION

Mankind has always been fascinated by the idea of tissue/organ generation and regeneration.

In the Biblical Book of Genesis, God created man from the dust of the ground and the first woman from Adam's rib. In the Greek myth of the titan Prometheus, he moulded men out of water and earth and defied the gods by stealing fire and giving it to humanity as civilization. He was then chained by Zeus, as punishment, up to the Caucasus rocks, where every day an eagle devoured his liver, which would regenerate overnight. The Holy Rig Veda (among the oldest religious texts in the world, composed approximately 2000-1000 BCE but also based on earlier oral traditions) contains the first mention of prosthetic and TE (Tissue Engineering): Queen *Vishpala*, who was amputated in a battle, was fitted with an iron leg enabling her to return to the battlefield. In Sumerian mythology the gods Enki and Ninmah created humans from the clay of the Abzy, the fresh water flowing underground. Human attempts to substitute injured tissue/organs or at least to restore their function, led to the creation of first biomaterials through History; defining a biomaterial as any material in contact with a human tissue intended to substitute or restore a lost function, we can find some examples in sutures or foot prosthesis applied in Ancient Egypt; dental replacement by seashells in Mayan population (ca. 600 BCE); hand prosthesis during the Middle Age to endosteal dental implants within the middles of the last century.[1,2]

Kam W. Leong, editor in chief of Biomaterials, offers a valid current definition of biomaterial as "a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure".[3] Thus, the current use and creation of a biomaterial is far from the first inert materials interfacing human body. As in the definition, a biomaterial is something that has been engineered, meaning that the final product has been modified by the addiction/subtraction/substitution of small functional moduli, as the gears of a clock. Biomaterials can be synthetic (i.e. polypropylene, polytetrafluoroethylene, polyethylene glycol, pyrolytic carbon, etc.) or biologic (alginate, collagen, extracellular matrix etc.). Both types of biomaterials show pros and contras, which discussion is not in the scope of this review. However, chemistry played and is still playing a fundamental role in the creation and technological development of any type of engineered biomaterial. Currently, many traditional biomaterials, with well proven mechanical properties and long history of clinical use, are subjects of surface engineering to enhance biocompatibility and ability of use in customized process. This surface engineering uses several different approaches from simple physico-mechanical treatment and surface chemistry up to nano-structurization. Biomaterials are one of the key elements in the triad underling TE approach being the other two stem/progenitor cells and bioactive molecules (i.e. GFs, chemokines and cytokines, fatty acids, miRNAs and any molecule able to activate, modulate and control a cellular response). For this reason, chemistry has also a pivotal role in TE. Despite the significant progress *in vitro* and *in vivo* on animal models, the achievement of the desired clinical and commercial deliverables has been frustrating, especially in diseases that cannot take advantage but from TE therapies.[4] In addition, the costs of such biotechnology may represent a further barrier for the future clinical diffusion. Indeed, sustainable TE may not be achievable with current approaches. Thus, it is our opinion that a strategy and methodology rethinking are needed, for promoting more inclusive and economical sustainable development together with a low environmental impact. Sustainable development of TE requires redesigning many chemical processes, which often rely upon technology developed in the 20th century and creating new reactions and protocols under less environmentally harmful conditions, using safer materials and studying more economically affordable translational technology to face diseases not treatable with current available medicine.

In this review we want to highlight the contribution that both "click", and "green" chemistry may represent for the development of new technologies in the TE field. Click chemistry is an approach described by Barry Sharpless in 2001 (Nobel Prize in 2001 for developing chirally catalysed oxidation reactions) based upon the following criteria: "the reaction must be modular, wide in scope, give very high yields, generate only inoffensive by-products that can be removed by non-chromatographic methods, and be stereospecific. The required process characteristics include simple reaction conditions (ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, use of no solvent or a solvent that is benign (such as water) or easily removed, and simple product isolation."[5] Thus, click chemistry meets the concept of green chemistry. Green chemistry is a philosophy based on 12 principles oriented to reduce waste and product toxicity, use renewable source materials and save energy.[6] In this review we would also like to give a warning about the possible wealth "divide" and generation of inequality caused by the technological advanced techniques such TE and how improvement in scientific fields of research should be oriented to challenge the gap with developing Countries.

## 2. CLICK CHEMISTRY CONTRIBUTION TO SUSTAINABLE TISSUE ENGINEERING

Most of strategies developed in the click chemistry can serve as an essential approach of green chemistry. The focus of click chemistry is on reducing the environmental impact of working with potentially toxic materials. This approach is based on chemical reactions which can take place in mild conditions but with a high efficiency, allowing the reaction between several chemical groups to realize a stable product not subject to oxygen reactivity.[5] Such reactions are also defined orthogonal, intended to avoid other side reactions, since bioactive molecules can present complex structures.[7] Indeed, bio-orthogonal chemistry refers to chemical reaction that can occur inside living systems without interfering with native biochemical processes. The recent development of copper-free click chemistry allows forming TE materials without the use of toxic catalysts or immunogenic enzymes that are commonly required.

### *2.1 Biomaterials and 3D printing tools*

One of the major issues in TE is the choice of scaffold biomaterial guiding the regeneration process. Among biomaterials, synthetic polymeric ones have had a wide success in TE because their characteristics are well defined, largely reproducible and possess strong mechanical resistance, even if they showed very low or no consistent bioactivity.[8] However, synthetic polymers may not represent a suitable biological microenvironment for i) host stem cells recruitment, ii) providing appropriate cues to promote asynchronous stem cells division and differentiate some of them, iii) promotion of angiogenesis and innervation. Synthetic polymeric biomaterials can be made biologically active through the functionalization with biomolecules (i.e. cytokines, drugs, fatty acids, GFs and miRNAs and many others). Previously described click chemistry approach has been applied to for the creation of biomolecule-polymer hybrids.[5] The most famous click reaction has been the CuAAC that, however, suffers from the uncontrollable accumulation of Cu ions within the biomaterial.[9] Thus, click chemistry rapidly evolved towards copper-free reactions. Diels-Alder (DA) reactions (Nobel prize in 1950) involve diene and alkene as reactant in water and give high efficiency and selectivity. Importantly these reactions will not produce toxic products.[10] One of the most common applications of DA reaction is hydrogels generation for TE. Hydrogels can be easily injected because the gelation usually occurs at body temperature, can be loaded with hydrophilic molecules and are particularly suitable as environment for highly hydrated tissues, such as cartilage. A hydrogel for cartilage TE was developed through DA reactions between hyaluronic acid (HA) and furan adipic dihydrazide and between HA and furan aldehyde, followed by PEG addition.[11] This hydrogel showed the same compressive modulus during the healing process, it was adhesive to cartilage because of the aldehyde-amine Schiff-base reaction and it also behaved as smart biomaterial, since it was able to change the structure in response to pH variations.[11] Hydrogel biomaterial application is not limited to hydrated tissue but can also serve as 3D environment to guide the differentiation of stem cells toward a desired tissue. A PEG-based hydrogel releasing dexamethasone, obtained by DA reactions, has been studied as 3D environment to induce MSCs to form bone tissue. MSCs cultivated within this hydrogel showed a high alkaline phosphatase activity and mineralization,[12] which could represent a first evidence of bone differentiation. Also *in vivo* a hydrogel created through DA reactions was studied for bone regeneration in rat cranial defects, showing bone formation after 12 weeks. This hydrogel was built up by the crosslinking of modified sodium alginate, bioglass and chondroitin sulphate.[13] Hydrogel biomaterials created by DA reaction found a plethora of applications, not limited to skeletal tissues. For example, cardiomyocytes were loaded in a hybrid hydrogel created by the application of DA reactions involving modified

PEG and fully interpenetrating thermosensitive hydrogel based on chitosan. The hydrogel/cardiomyocyte graft was implanted subcutaneously in nude mice and allowed for cell retention and survival for 2 weeks. This hybrid material kept the robust mechanical properties obtained by DA reactions and accelerated gelation *in situ* thanks to the thermosensitive counterpart.[14]

SP-AAC (strain-promoted azide-alkyne cycloaddition) is another copper-free click reaction, in which the ring strain accelerates the reaction between cyclooctyne and azyde.[15] Several hydrogels of modified PEG, HA and dextran for biomedical purposes (bone, cartilage and neural regeneration) have been created with this approach. Major advantages of these hydrogels are the possibility to customize biomaterial properties directly *in situ,* the functionalization with bioactive molecules and photo-patterning in the presence of live cells.[16,17,18,19,20,21]

Sometimes hydrogel biomaterials do not offer the required mechanical strength because of their own nature. Cross-linking is a strategy adopted to enhance mechanical strength of biomaterials. The series of reactions involving thiyl and carbon-based radicals in a basic solution leading to the formation of covalent carbon-carbon bonds are known as thiol-ene click reactions and has been used in the development of cross-linked hydrogels.[22] Applying this strategy, a hydrogel has been created, that can be degraded in a tubular structure when exposed to glucose. Such a hydrogel is suitable in neural system regeneration and has been studied as a scaffold material for endothelial and neural stem cells for the creation of a neural like tissue.[23] Recently, the possibility to link a hydrogel with live cells (C2C12 myoblasts) has been demonstrated.[24] In this study both alginate, as backbone of the hydrogel, and myoblasts have been modified with chemical groups able to give rise to a thiol-ene reaction. The main limitation of these reactions is the need of an activator of the catalysis, like UV radiations or photo-polymerization, which poses biological concerns. Similar reactions, called thiol-Michael reactions, do not need such activators and are permissive towards several chemical groups.[25]

Less frequently TE has taken advantage of click chemistry for the creation of biomaterials other than hydrogels. For example, Poolman et al. generated a film of polyacrylic acid which thickness and morphology can be tuned controlling the density of the reagents through a layer by layer method.[26] Microspheres represent another scaffold conformation particularly suitable as a carrier for bioactive macromolecules. Microspheres based on cross-linked poly(divinyl benzene) have been functionalized by DA reactions to bind poly (ε-caprolactone) and fluorescent Rhodamine-B.[27]

Biomaterials should support functional tissue regeneration also guiding cell proliferation and differentiation in the suitable 3D environment. The 3D structure assumes a critical importance during the regeneration of highly hierarchically structured tissues/organs, such as skeletal muscle, heart, lungs or kidney, where the 3D architecture is essential for organ own function. Three-dimensional bioprinting is trying to meet this challenge. What is used as bioink to print the final tissue structure should meet several parameters: to be biocompatible, not cytotoxic, and rapidly form the final product (e.g. by gelation). Bertlein et al. created a bioink, called GelAGE, obtained by the polymerization of allylated gelatin through thiol-ene click reactions that can be activated both by UV-light and visible-light.[28] Same type of click reactions has been applied for creation of linear poly(glycidol) based bioink that polymerized under UV-light. The final product was a 20-layer structure enriched with hyaluronic acid with a height of 3.90 mm.

Click chemistry has been fundamental in TE not only for the improvement of biomaterial performance but also for the creation of other tools such as bioink in 3D printing technology, drug delivery and tracking of drugs during release. Chemical reactions and molecules involved in click chemistry are extensively described in a review by Zou et al.[7]

### *2.2 Living cells engineering*

Click chemistry can also be a useful tool for engineering living cells to allow the modification of cells with chemical tags. Using tagged biomolecules, we can introduce chemical tags into proteins, glycans and lipids in living cells that metabolize such biomolecules releasing the tag. Tagged biocomponents can then be exploited for several purposes as cell tracking, cell drug delivery, cell complex, tissue targeting, and tumour labelling.[29]

Click chemistry in living cell engineering is an important application in cell transplantation or cell-based therapy. This latter approach represents a powerful therapeutic method for the treatment of many diseases. However, the therapeutic outcome has not been always successful, due to low engraftment rates or short cell survival after transplantation. In addition, the biodistribution and fate of transplanted cells are not easy to follow due to the inadequacy of *in vivo* cell tracking methods. Thus, to improve these biases, cells functionalization and tracking techniques, through cell engineering, by click chemistry for example, have been introduced. The first application of click chemistry in cell transplantation for taking the transplanted cells was carried out in 2014 by Kang.[30] This approach was based on SP-AAC reaction aimed at engineering cell surface with N-azidoacetyl-mannosamine ($Ac_4ManNAz$) that offers the link with the probe. This approach was then improved in order to stabilize the tracking for longer time (4 weeks), to avoid the impairment with cellular functions, and to make the tag detectable through different technologies, i.e., fluorescence, computed tomography and magnetic resonance.[31,32] Click chemistry-engineered cells have found an important application also in other fields as the cell-based drug delivery.[30] MSCs are known to be attracted by tumours, thus MSCs have been investigated as an anti-cancer drug carriers.[33] Cell surface modification using metabolic glycol-engineering and copper-free click chemistry has been used for the functionalization of MSCs with NPs.[31] The authors demonstrated that the combination of metabolic glycol-engineering and the SPAAC reaction allowed for the modification of MSCs with CNPs (chitosan NPs) in a short reaction time, and that CNP-modified MSCs could be tracked over long-term.[31] If click chemistry for glycoengineering can be selectively applied to tumour cells it could be possible to functionalize tumour cells with receptors for a specific anti-cancer drug[34] or to express immune-stimulant molecules.[35] $Ac_3ManNAz$ has been synthetized linked to a substrate that can be cleaved by enzymes highly expressed in different tumours[36,37,38] allowing for tumour labelling.

## 3. GREEN CHEMISTRY CONTRIBUTION TO SUSTAINABLE TISSUE ENGINEERING

Another issue related to TE is the sustainability in terms of environment and economic sustainability (discussed in paragraph 4). Increasing interest about sustainability in each aspect of individual and society life is now rightfully paid by several Countries all over the world, especially in the European Union (Transforming our world: the 2030 Agenda for Sustainable Development[39]). The extremely rapid climate change, the consequent environmental mutation and species extinction[40] urge the need for a green approach not only in consumables, transports and energy production, but also in biomedical research. Green chemistry is defined in 12 principles by Anastas and Warner (1998).[6] Here we report the principles as described by Linthorst:[41]

1. It is better to prevent waste than to treat or clean up waste after it is formed;
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product;
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment;
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity
5. The use of auxiliary substances (e.g. solvents, separation agents) should be made unnecessary wherever possible and innocuous when used;
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure;
7. A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable;
8. Unnecessary derivatization (blocking group, protection/deprotection, and temporary modification of physical/chemical processes) should be avoided whenever possible;
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents;
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products;
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances;
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

In TE, attention is arising to the use of chemical products that are safe and green, to their substitution with green strategies, and to the obtainment of final products which by-products and disposal are not hazardous for the environment and human health.[42] Indeed, the creation of several biomaterials requires steps involving cytotoxic solvents, such as the electrospinning of collagen fibres. Electrospinning is a very popular technology to form micro- and nanofibers starting from polymeric mats melted or in solution. Polymeric mat is loaded in a syringe whose needle is directed toward a metallic rotating support; both the support and the needle are subject to high voltage field that generate an electrostatic force; when the electrostatic force overcomes the surface tension of the polymeric mat, the fibre starts to form.[43] Most of the solvents used in electrospinning are organic, cytotoxic and harmful for human health, hence the study of green solvent to be used in biomaterials generated via electrospinning.[44] Zhou et al. developed collagen-I fibres dissolved in phosphate buffered saline/ethanol solution, thus avoiding the application of cytotoxic organic solvents. Such collagen fibres also brought HAP microspheres for bone regeneration.[45] HAP for bone regeneration is also produced in nanoparticle size, because NPs resemble the native crystalline structure of bone ECM. A green synthesis of nano-HAP has been obtained starting from eggshell waste as source material for calcium, while phosphate was obtained from ammonium dihydrogen orthophosphate.[46] Another green strategy to obtain nano-HAP is based on a backbone of fatty acids (linoleic, lauric and oleic acids) for HAP formation.[47] PUFAs, namely linolenic acid, present in flaxseed, has been demonstrated to counteract the negative effects of TNF upon myoblasts *in vitro* and the degeneration of myofibers in muscular dystrophy *in vivo*.[48] This study suggested that PUFAs could represent green bioactive molecules to be loaded upon biomaterials for skeletal muscle regeneration. Thus, PUFAs can be green candidate molecules to be used with different purposes in TE.

The natural protein silk fibroin is probably one of the most known natural biomaterials ever studied. Silk fibroin results particularly suitable as biomaterial in tissue regeneration because of its high biocompatibility and good mechanical properties, indeed it has been customized in several forms for different applications in TE.[49,50,51,52,53] A hybrid biomaterial composed by silk fibroin and graphene oxide (GO) has been created using a green method involving silk crystallization through glycerol during lyophilization, thus avoiding organic solvents. Aiming at bone regeneration, this hybrid biomaterial was loaded with simvastatin that enhanced the production of BMP-2.[54] Another green and natural source for the fabrication of biomaterials is represented by polysaccharides, abundant in nature. Recently, a composed nanofibrous biomaterial for skin regeneration has been developed via electrospinning of polysaccharides extracted from *Beta Vulgaris* together with nylon66. The presence of the polysaccharides contributed to make the biomaterials more hydrophilic. This biomaterial was able to maintain the functionality of the seeded keratinocytes.[55]

A careful observation of the natural world often inspires scientists for the creation of new biomaterials with innovative, green and affordable characteristics. It is the case of biomaterials incorporating PDA, a polymeric oxidation product of dopamine, inspired to the dopamine produced by mussels, able to adhere to several materials. PDA has been incorporated in a hydrogel of chitosan and graphene studied as conductive material for cardiomyocytes cultivation. This biomaterial enhanced cardiomyocyte proliferation and spontaneous beating rate.[56] Natural molecules have been studied as 3D culture environment mimicking the ECM. A collagen/heparin hydrogel able to immobilize growth factors has been evaluated as 3D culture environment for neural stem cells. In this environment neural stem cells formed synaptic connections and showed electrical activity. Furthermore, the cells within the 200 μm thick hydrogel could easily detected at a phase-contrast microscope.[57]

Nanomedicine is another field where green chemistry is capturing an increasing attention. The development of NPs is extremely important for efficient and targeted drug delivery, in particular but not limited to cancer treatment. However, the production and also the use of NPs can produce hazardous molecules and have negative effects for human health both at a molecular and cellular level.[58,59] Cellular and subcellular mechanisms of interaction with NPs have been studied only recently.[60] The use of NPs has been associated with cell detachment consequent to disruption of tight[61] and adherent[62] junctions or reduced amount of vinculin at focal adhesion.[63,64] NPs have also been demonstrated to perturb cytoskeletal integrity and function, inducing the formation of aberrant actin forms.[65,66,67] NPs cell treatment has also been associated with a decrease in cell motility that can be an adverse effect in healthy cells, but is advantageous in the treatment of cancer cells reducing the possibility of metastasis.[68,69] Nano-materials customized in 2D films has been developed as photo-thermal convertor for the minimally invasive near-infrared (NIR) laser-induced tumour PTT. Li et al. produced a bi-dimensional nano-sheet of $MoS_2$ incorporating soybean phospholipid that confers colloidal stability to the nano-biomaterial. Soybean phospholipid extraction can be done on a large scale and at a low cost since it is present in several plants. Soybean phospholipid incorporation follows an easy processing, unfortunately involving chloroform; moreover, the excess can be dispersed simply by water washing. $MoS_2$ nano-sheets have been covered by a soybean phospholipid layer to generate a platform for breast cancer photothermal therapy.[70] Thus, the soybean phospholipids represent a green source for biomaterial creation.

NPs were also obtained via a green process by mixing chitosan and GO in aqueous solution and acetic acid, then rectorite was added to enhance drug encapsulation of doxorubicin hydrochloride for cancer treatment.[71] A nano-hydrogel has been created with a simple heating step, without any additional chemical reaction, to denature lysozyme mixed with sodium carboxymethyl cellulose. The nano-hydrogel has been tested for the release of 5-fluorouracil, which release was decreased in stomach and accelerated in intestine, thus protecting the drug through the gastro-intestinal apparatus until the release within the intestine.[72]

Soluble GO is usually obtained by the reaction with hydrazine and hydrazine hydrate which are toxic. A cost-effective and green method has been developed to produce soluble graphene oxide using *Bacillus marisflavi* as a reducing and stabilizing agent at 37 °C in aqueous solution and mild conditions.[73] GO can be reduced in order to eliminate oxygen groups and obtain a planar conformation,[74] thus allowing for incredibly high drug loading efficiency. A green method to obtain reduced-GO used riboflavin-5'-phosphate sodium salt dehydrate. The obtained NPs were tested as pH-responsive carriers of doxorubicin hydrochloride and showed high bonding efficiency, high stability and effective drug release at pH variation.[75] Similarly reduced-GO has been obtained in eco-friendly, one-step methods using biomolecules such as alanine,[76] L-cysteine[77] and L-tryptophan together with ascorbic acid and NaOH.[78] NPs of silver nitrate and gold chloride can be prepared through safe, cost-effective and eco-friendly natural materials. Nano-spheres of $AgNO_3$ have been obtained in aqueous solution by mean of egg white,[79] while NPs of trivalent aurum can be prepared in concentrated broths of seaweeds extracts, both investigated in cancer treatment.[80] Silver NPs for drug delivery has also been obtained by *in situ* reduction using *Azadirachta Indica* and then loaded onto a hydrogel prepared through the environment friendly process involving cross-linked poly(acrylamide) and a rapid redox polymerization with N, N'Methylenebisacrylamide in the presence of carboxymethylcellulose.[81] Silver NPs both spherical and cubic has been prepared using another fast and green approach, based on the use of light ($\lambda$ = 420 nm) to catalyse the reaction, that requires 10 minutes. Such Ag-nanoparticles showed a good antimicrobial activity and a dose-dependent cytotoxicity.[82] Interestingly, NPs incorporating an anti-tumour drug have been obtained by the self-assembly of ginsenoside, extracted from *Panaxginseng*. Ginsenoside NPs showed a higher efficacy of delivery, if compared to the free drug, and a prolonged half-life in circulating blood.[83] Protein extract from plants has also been investigated as wound dressing biomaterial. Fibrous biomaterials from soy and corn zein have been fabricated via electrospinning. Soy derived biomaterial supported the growth of human dermal fibroblasts and in both biomaterials ECM protein deposition was observed.[84] Genipin, obtained from geniposide, present in the fruit of *Gardenia jasminoides* has been cross-linked with gelatine and loaded with silver nanoparticles by heat treatment and UV-light, avoiding the use of solvents or reducing agents, with the aim to create a biomaterial showing antimicrobial activity. This green biomaterial resulted successful against *Staphylococcus aureus* and *Escherichia coli* but not against *Candida albicans*.[85]

Green chemistry is not only contributing to the technological development of tools for TE purposes, but also guiding society toward a more sustainable research in term of less toxic reagents/products, more cost-effective materials, sustainable sources and energy use.

## 4. CHALLENGING THE GAP WITH DEVELOPING COUNTRIES AND AVOIDING DIVIDE BY BIOTECHNOLOGY IN POLARIZED SOCIETIES

It is of paramount importance to understand and predict the impact of the cost of products and technologies related to TE and regenerative medicine (including a variety of products, e.g. biomaterials, stem cells, bioactive compounds), in a society where a wealth polarization is increasingly emerging. Indeed, the expensiveness and high technology involved in this area of research, as well as other biotech clinical application, represent a big concern and create a tremendous response among scientists. This issue poses also an ethical problem due to the responsibility to address the increasing rate of diseases in the developing Countries and their limited funding for facing them with biotech medical treatments/devices. Thus, all the efforts must be devoted to assessing programs of cooperation that will lead to a more inclusive society with equitable access to benefits and reduce inequalities driven by the technology divide in this area of research. Otherwise the advancement of such science can be perceived as excluding and ultimately as a new divide. Despite the European Commission has paid attention to the development of an inclusive society, promoting this initiative within the Horizon 2020 Program, involving also the scientific area, e.g. through the actions Support to Open Science, Open Access and Open Data (see the Work Program 2018-2019 *Europe in a changing world – Inclusive, innovative and reflective societies*), the advances done in the direction of a sustainable and inclusive science are not sufficient.

Another major concern is related to the lack of regulatory standards among the Countries in a globalized world. It may also occur that no standard for safety, quality and efficacy of TE and regenerative medicine products is present and this creates a safety gap among Countries leading to adverse effect on human and environment health.

## 5. CONCLUSION

Over the last years tissue engineering and regenerative related approaches have accelerated through the introduction of more advanced tools, resources and methodologies. The ability to combine chemistry and biology toward a more sustainable development is attracting research, industry and society. During the last decades the application of click chemistry to the development of TE related tools allowed extraordinary technological advancements. Green chemistry, that is also included in some click reaction methods, represents a challenge for TE and regenerative medicine, claiming more attention for a sustainable development of methods and products, and asking for a paradigm shift aimed at simpler, safer, cheaper and yet technologically advanced methods and products. There are all the conditions for this transformation.

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# Chemistry Beyond the Book: Open Learning and Activities in Non-Formal Environments to Inspire Passion and Curiosity

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**Abstract.** Several scientific channels on TV, crowded scientific fairs, and many serious scientific board games on the market demonstrate that people are curious about science. However, when asked about the perception of scientific subjects, Chemistry in the first place, general public still shows rejection toward "too complicated", "abstract", and "far from everyday life" topics. Unarguably, every Chemist would not recognize Chemistry as neither "abstract" nor "far from everyday life": actually Chemistry, the so-called central science, is all around us. Where is the gap to fill, then? Why are not we able to convert that innate curiosity, which makes people stepping out from their houses to join public engagement activities, into genuine, time-persistent, passion about Chemistry? Such questions will be addressed herein, giving practical examples of possible approaches to address the problem. Special emphasis will be given to new learning means, generically referred as "Open Learning" ones, and interactive teaching approaches typical of non-formal environments, such as Science Festivals. Real examples of activities beyond the formal curricula of chemical study, some carried out by us in the framework of the "*Diffusione della Cultura Chimica – Società Chimica Italiana*" (Dissemination of Chemical Culture - Italian Chemical Society) mission and vision, will be discussed underlining their role in enhancing learning and inspiring confidence and passion toward Chemistry.

**Keywords.** Open Learning, Chemistry, Society, Gamification, Science Festival, Didactics, Interactive Teaching Approaches.

## INTRODUCTION

The *IdeenExpo 2019* in Hannover (Germany) had about four hundred thousands visitors in eight days,[1] the 30th edition of the *Edinburgh International Science Festival* (Ireland) in 2018 had about one hundred seventy five thousands visitors in two weeks[2] and the 16th edition of the *Science Festival*

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*in Genoa* (Italy)[3] in 2018 reached about one hundred fifty thousands people in ten days. These are just few examples of recent big scientific events promoted by scientists and scientific organizations to increase the public engagement and the public understanding of the crucial role of Science in the modern Society.[4] Science Festivals are typical non-formal contexts, where different scientific and technological aspects, innovations and even new scientific concepts, are shown in a spectacular way with several purposes: impressing people about the beauty of science, increasing their interest and curiosity through science, giving the sense of the pervasive presence of science in every-day life.

Among different scientific disciplines, Chemistry is usually present in Science Festival, even if not predominant, except in few cases (see, for instance, the Italian *Festival of Chemistry* organized by the University of Basilicata, since 2009).[5,6]

Despite Chemistry is recognized from the scientific community as a "central science", since it connects different disciplines and most of the basic chemical concepts are fundamental in Biology and Medicine, Nanoscience and Material Science,[7] the general public perception of Chemistry is quite far from this idea.[8]

Chemists have defined a specific word, *Chemophobia,* to describe an "*irrational aversion to or prejudice against chemicals or Chemistry*".[9] "*More specifically it refers to the growing tendency for the public to be suspicious and critical of the presence of any man-made (synthetic) chemicals in foods or products that they make use of*".[10] While demonstrating the various origins of *Chemophobia,* as a quite complex human attitude, goes far beyond the scope of the present work, it is worth noticing that several recent studies have systematically investigated the public attitude toward chemists and Chemistry giving rise to interesting results.[11-14]

According to the survey proposed by the Royal Society of Chemistry (RSC) in U.K., Chemistry is often perceived as "abstract", "difficult" and "far from everyday life".[14] However, most of the interviewers did not declare any pre-conceptual aversion or any *Chemophobic* attitude towards chemicals and chemists, so the general perception of Chemistry among the lay public is more positive than what expected by chemists themselves. Although the RSC study paints a better picture than the chemists themselves had expected, it also revealed a sort of "emotional neutrality" and a "lack of engagement with" Chemistry.[12]

Another interesting result coming from these studies is related to the interviewers' school experiences about Chemistry;[12,13] most of them declared that their experiences at school were indeed crucial in determining their ideas about Chemistry. These are some of the interviewers' statements concerning how Chemistry was taught at school, based on their own experience: "*chemical concepts were too abstract*", "*few examples about every-day life applications of Chemistry were done*", and "*the utility of Chemistry was not addressed*". [12,13]

The evidence of a link between the formal and traditional teaching of Chemistry and the diffuse perception of a distance between chemical concepts learned at school and the role of Chemistry in the Society could be a good starting point to rethink the teaching approaches to Chemistry. Moreover, as suggested by RSC, instead of focusing on the minority of negative views, the scientific community, and in particular the chemists, should try to address the substantial indifference or lack of engagement in order to improve the image of Chemistry.

According to these indications, the biggest challenge seems to be how to convince students and the general public on the relevance and the utility of Chemistry. We need to foster public excitement in Chemistry by making the public aware of the extent to which Chemistry is indeed all around them. However, this ambitious objective can only be reached by working on different parallel targets:

1. Changing the way Chemistry is taught at school;
2. Establishing stronger connections between the research in Chemistry and the Society;
3. Talking more about applications of Chemistry than theory and abstract concepts;
4. Using the digital tools, by exploiting their potentialities to increase the knowledge of Chemistry;
5. Enhance the communication skills among young chemists and take advantages from the non-formal learning environments.[15,16]

A possible mean to achieve these tasks is the so-called Open Learning, concept with a broad meaning usually referred to activities and teaching strategies that enhance learning opportunities beyond formal education systems. Open Learning is just an appendix of the broader Open Science movement, the ongoing transition promoted by the European Union (EU) in how research, knowledge and scientific culture is performed and disseminated by using digital technologies and new collaborative tools.[17] On the other hand, Open Learning is related to the so called *Life-Long* learning strategy, which became central in the EU program for the education of new European citizens since 1985.[18] Several studies have indeed underlined how the learning of science, and of Chemistry in particular, is a complex process extended to the whole life, resulting from a continuous interplay among learning in formal, non-formal and informal contexts.[19] The role of non-formal and informal contexts in learning Chemistry, such as the experiences of interactive laboratories in science museums and science festivals or activities about Chemistry through mobile devices (m-learning), internet (e-learning), wikipedia and other digital tools, has been recently overviewed by several authors.[20-22]

In this paper, we will focus on some experiences related to different Open Learning strategies, divided in two subsections: *i.* Chemistry in the Arena and *ii.* Chemistry, new media and gamification. In particular, we will describe and comment real examples on how different Open Learning approaches have been successfully applied to foster trust in the essential role of Chemistry for our Society and ultimately inspire passion and curiosity toward this subject.

## OPEN CHEMISTRY AND OPEN LEARNING IN CHEMISTRY

Open Science is a comprehensive reform proposed and promoted by the EU on how science can be practiced in an accessible, transparent and reusable way in the current digital age.[17] Considerations about which technological changes can we expect from this reform and which impact will Open Science, and in particular Open Chemistry, have on both Society and the research community have been extensively discussed elsewhere.[23]

Among the Open-components enabling such historical transition in Science, we find the promotion of free access to scientific literature and data sets (i.e. Open Access and Open Data, respectively), as well as freely available teaching and learning materials, which hold the promise of reducing financial and structural barriers and bridging the gap between the less and more developed countries, especially in fields where small investments can have relevant social impacts, as Chemistry is (see, for instance, the Open Educational Resources[24-27]). As a consequence, such shift also impacts teaching and learning activities, which are being redefined under the concept of Open Learning.

Open Learning, grounded on the work of pedagogues and educational reformers like Célestin Freinet and Maria Montessori among others, emerged as teaching method in the late ‘70s. Starting from the statement that students of the same age have vast differences in experiences, interests, and competencies, and that such differences play a crucial role in the learning process, the key concept of Open Learning pedagogy is an “independent and interest-guided” learning.[28] This can be achieved by means of interactive learning, interdisciplinary focus activities, hands-on experiences, group-based dialog formats, evidence-based problem analysis, and by developing and using open educational resources. Beside the chosen mean, the final goal is to enable each individual learner to be self-determined, confident, thus genuinely inspired by the learning process.

From the scientists’ perspective, this translates into moving away from what has been defined as the “deficit model” of public attitudes towards science.[29] The traditional idea that public scepticism about science is the result of a lack of understanding, and can only be filled by providing information, is nowadays replaced by a “dialogue model” that engages publics in two-way communication aimed at disseminating the social implications of science.[15-17, 30, 31]

In this context, science festivals, open-lab activities, science gamification using new media and similar learning opportunities beyond formal education systems can be applied to bring back the public perception of Chemistry as central science for the development of our Society. These aspects will be discussed in details in the following sections.

Focusing on Chemistry, several examples of Open Learning teaching approaches successfully proposed to students are those related to new open digital environments and platforms, such as the so called Schnaps,[32] which was developed to help students to approach Chemistry with the problem-solving method. Similar strategies have also been explored related to specific topics in Chemistry, such as environmental applications of Analytical Chemistry.[33]

The use of virtual laboratories and digital tools to teach Chemistry has also been object of intense research about the effectiveness of MOOC (Massive Open Online Courses), which were developed for the first time in the 2002, by the Massachusetts Institute of Technology with the OpenCourseWare («MIT OCW») project. Despite of the first official MOOC were open in 2012 by the major American scientific universities and research institutes, the number of MOOC about Chemistry represents less than 5% of all online courses. Nowadays, several studies have been published putting in evidence the role of such interactive and participating learning platforms to enhance the learning of Chemistry among undergraduate and high school students.[34-36]

Besides assessing how interactive and participating learning platforms impact on students, another question arises: are teachers ready and minded to embrace this cultural transition? Luckily, for teachers passionate about and who wants to get trained on such Open Learning and innovative didactics, dedicated initiatives have been proposed in recent years. For instance, “Playing with Protons” is an education initiative led by the CMS experiment at CERN bringing together primary school teachers, science education specialists and CERN researchers to develop creative approaches, learning activities, hands-on experiments with everyday materials to help all primary students engage effectively in science, discovery and innovation.[37] This growing community of passionate, innovative and creative primary school teachers get free access to learning resources, share classroom activities with like-minded colleagues and create opportunities for school-to-school collaboration, paving the way for a full exploitation of Open Learning.

## I. CHEMISTRY IN THE ARENA

Science festivals, nowadays taking place all over the world[1-7], aim at disclosing and disseminating the role of science in the Society and the relationship of science with different aspects of everyday life. This effort in bringing science "out of the laboratory" and in engaging with the public in a constructive dialogue is the key of the success of such "creative, playful and surprising celebration of science".[4]

A typical science festival comprises a wide variety of events ranging from hands-on activities, spectacular demonstrations, workshops and conferences up to the involvement of arts.

The presence of Chemistry in science festival, although rarely predominant[5], is pervasive and undoubtedly among the most spectacular for the general public. Indeed, at first sight, solutions suddenly changing colours or matter changing its state appear as magic and almost unbelievable phenomena. Also simple laboratory equipment, like a magnetic plate with a bar stirring a methylene blue-containing solution, inspires curiosity in the public by evoking a charming world disclosed to only few people.

This is also the reason why the ancestors of modern chemists, the "alchemists", were considered halfway between philosophers and magicians. Indeed, Chemistry became a science only in the middle of the 17th century. Before this date, it was a wide cluster of practical knowledge as leather tanning, metallurgy, fabric dyeing, and many other craft activities. More or less everywhere, several centuries before Christ, the carbonate rocks were heated and milled to produce lime to built houses. The famous painters like Leonardo da Vinci (1452-1519) or Michelangelo Buonarroti (1475-1564), started their careers by preparing pigments for example by roasting and milling teeth (black), or earths (terra di Siena) and mixing them with rock powders, such as the orange cinnabar or the light blue lapis lazuli, and binders in the laboratory of their masters. On the other hand, one century ago, every woman was able to produce soap from grease and ash. Those are just few examples of chemical reactions!

So, science festivals are the perfect occasion to make the general public aware of the central role of Chemistry in our Society and remembering them how pervasive it has been for human life and culture throughout history.

Even with very simple chemical concepts and means, one can inspire interest about Chemistry and research, fascinate kids, and motivate teens to start looking at Chemistry as a key to open the secret behind the technology they are using on a daily basis. In other words, such activities in science festivals increase critical thinking and implicitly communicate that Chemistry is not just a bunch of formulas and numbers wrote on a book, but is a mean to interpret the world around us.

For instance, members of the group Diffusione della Cultura Chimica – Società Chimica Italiana attended multiple editions of the "Festival della Scienza di Genova", where several didactic laboratories were proposed, such as the laboratory about visible absorption spectroscopy("Fare Chimica con la Luce" – "Doing Chemistry with Light" – 2017 edition, theme: CONTACT). More recently the group itself promoted and realized a didactic laboratory using new technology as an appendage of analytical techniques to enable to "see" chemical reactions ("CIAK: (re)AZIONE!" – "CIAK: (re)ACTION!"- 2018 edition, theme: TRANSFORMATIONS).[4] In both cases, visitors were offered the possibility to engage with Chemistry by means of simple, but real experiments in a very interactive environment (Figure 1). For instance, the laboratory "*Fare Chimica con la Luce*" was a very effective activity to introduce students of the secondary school to a quite complicate subject of

**Figure 1.** Typical setting of didactic laboratories at the "Festival della Scienza di Genova", 2018 edition.

Physical Chemistry: molecular spectroscopy.[38-40] This particular "format" was also tested with students visiting the University under the Educational Orientation programs, such as "PLS" (Piano Lauree Scientifiche), with the aim to get students interested in scientific studies.[41] The use of portable spectrophotometers developed for educational purposes or the development of prototypes of colorimeter to measure coloured solutions directly by the students provided to enhance the understanding of some basic concepts of molecular spectroscopy.[38-41]

"CIAK: (re)AZIONE!", designed by members of the group *Diffusione della Cultura Chimica – Società Chimica Italiana,* was another good example of interactive activity related to the concept of "chemical transformations" and the interplay between Chemistry and technology, where kids (and adults, too!) were captured by the phenomenological changes occurring during a chemical reaction.[42,43] People who participated to the lab was helped in understanding the basic of why and how matters change colours or state of matter, and choose the most appropriate mean to visualize such changings thanks to the digital devices (i.e. tablet or smartphone, Figure 2). In all cases, after a first feeling of surprise and amusement, we notice that students and general visitors focused on what was happening under their eyes and started somehow interiorize the scientific method by making hypothesis, testing, discussing the results and deciding how to proceed.

**Figure 2.** Primary school students performing and filming in slow-motion the synthesis of Prussian Blue during the laboratory "CIAK: (re)AZIONE!" at the "Festival della Scienza di Genova", 2018 edition.

Similarly, open-lab activities are organized to establish stronger connections between research in Chemistry and the Society and talk about applications of Chemistry in every-day life.

For instance, the "*European Night of Researchers*" is an event organized by the European Commission with the aim of celebrating the work of the researchers.[44] Every year, in the same day in September, every country proposes different communication, dissemination and public engagement activities organized by local universities, research centres, museums and schools. Perfect occasion also to enhance communication skills among scientists, such in-formal learning environments offer the unique opportunity to let the people enter real laboratories, meet researchers in person and feel free to ask them everything about their research (Figure 3). As reported on the official web-site[44], "*from 2018-2019, 55 projects have been implemented in 371 cities across Europe and beyond. During the 2018 Night, over 1.5 million of visitors attended!*". These numbers give the idea of the social impact of these activities and the high demand from the European citizen to participate and get involved in the science processes. Noteworthy, the goal of such activities is not to transfer information, rather to seed confidence and knowledge on how Chemistry could be useful to tackle different real-world challenges.

**Figure 3.** Activities during the European Researcher Night 2018 at the University of Pisa.

To summarize, with the aim of addressing the already discussed issue about the underestimated perception of the role of Chemistry in our everyday life, bringing "Chemistry in the arena" with science festivals and open-laboratories activities fulfil the Open Learning vision and mission.

## II. CHEMISTRY, NEW MEDIA AND GAMIFICATION

Knowledge can be considered as static, while the way in which information is transferred and then hopefully converted into knowledge is fluid and, nowadays, incredibly fast. According to a recent study on the Italian citizens habits, the 95% of Italians use smartphone and internet on a daily base, the 32% for most than 5 hours per day (even for longer if we consider teenagers).[45] Such scenario can be perceived in two opposite ways: either as a treat to the traditional, book-based teaching and learning approach, or as an exceptional opportunity for its enhancement. Indeed, trying to convey the interest of such users toward scientific discipline could be an opportunity.

Undoubtedly, the use of technology can help to increase science lesson engagement. Today's technology can provide an immersive experience and make learning a more active experience, stimulating students at a deeper level.

Strictly related to this, we find the concept of "science gamification": an approach for improving students' attitudes toward learning traditionally challenging subjects by proposing games, which increases engagement by means of rewards and feedback.[46] Far from being a simplified version of traditional education methods, the research agenda for the field of science gamification concerns with central aspects of research methodology, including psychometric measurement, experimental design, and generalizability, in order to maximize its trustworthiness and real-world value, as comprehensively discussed elsewhere.[47]

"Gamification" in education and "Cooperative Learning", where most of the activity is related to a team game, have proven successful in many contests.[48,49] Serious games about Chemistry have always existed and seem to be one of the more appealing and prone to popular marketization: in fact, "The Laboratory of Crystals", "Science and Lip-Sticks" and "Chemistry Lab" are only a few we can find in toy-shops.

Nowadays, with the diffusion of technology and the wide engagement of pupils and teenagers with new media and technology, science gamification is moving from the shelf to the smartphone.

An example is the popular Kahoot![50] game-based platform. With the claim "*make learning fun, inclusive and engaging in all contexts*", Kahoot! not only fully embraces the principles of Open Learning, but it also exquisitely merges the benefit of using new media (e.g., tablets, smartphones) for teaching and learning activities. With Kahoot! a teacher can create learning games (kahoots) by typing a series of multiple choice questions and optionally adding videos, images and diagrams to amplify engagement. Then, players (ideally, a class) answer the questions on their own devices, while games are displayed on a shared screen to unite the lesson. This cooperative learning creates what the Kahoot!'s authors define as "*campfire moment, encouraging players to look up and celebrate together*". Whether players are in the same room or on the other side of the globe, such game-based learning platforms also allow to search among millions of existing games and share results, thus enabling "Social Learning" which promotes discussion, pedagogical impact, and encourage players to deepen understanding, mastery and purpose, as well as engage in peer-led discussions.[51,52]

As reported by Jack Quinn, 5th grade teacher at Withcomb Elementary School (Houston, TX, USA), using such game-based learning "got students more plugged into learning, helped them improve mastery of complex science topics, and, as a result, they did 11.4% better in their exams compared to last year and are projected to grow 75% above the district norm".[53]

The *Diffusione della Cultura Chimica – Società Chimica Italiana* group recently used Kahoot! to disseminata the UNESCO international year of the periodic table (IYPT2019). In particular, a dedicated Kahoot! quiz for high school students was created by the *Consiglio Nazionale delle Ricerche* and proposed by the group during open days, career guidance, and PLS activities (Figure 4).[54] For instance, during the "Chemistry Days", a PLS

**Figure 4.** The "Human Periodic Table", performed by students attending the CNR event celebrating the International Year of the Periodic Table (IYPT).

event organized by the University of Palermo, the *Diffusione della Cultura Chimica* group proposed the quiz to 31 students at the end of a traditional talk on the history and curiosity on the Periodic Table. Questions ranged from simple notions (e.g., What is the surname of the scientist who first proposed the periodic table?) and curiosity on the origin of the elements or their names (e.g., Which among these countries was named by an element?), up to questions related to the presence of elements in everyday life (e.g., Which among these elements is not used to build a smartphone?). We noticed that by using their smartphones, even if for simply answering a question related to concepts they had just listened to or that were already aware of, students were fully engaged and almost anxious to give the right answer. Noteworthy, at the end of every quiz session, a report summarizing statistics on the overall and question-specific performances is available (Table 1). When the quiz is proposed after a lesson, such report can be used by teachers to evaluate the level of understanding of concepts proposed during the lesson. When the quiz is proposed before the lesson itself, in line with the "blind test" methodology which uses the feeling of initial failure as "cognitive need" (i.e., a stimulus to learn), the report can be used to finely tune the content of the lesson.[55]

Another example of interactive and participative activities, where the good use of digital tools and devices is crucial, is represented by the so-called "Citizen Science" programs.[56,57] These programs aim to reach a shared knowledge among citizens (of any age, culture and education) and about specific scientific topics, which are usually related to concrete everyday problems (such as environmental ones).[58] For instance, in the recent years, several "citizen science" programs were promoted by ARPAT[59], in Tuscany (Italy), to monitor the sea status during Summer time. Among these activities, people were invited to participate to the monitoring of a naturalistic area or an environmental phenomenon (such as the nesting of *Caretta caretta* turtles), by recording data, sharing comments, observations, images and videos, but also measuring some significant chemical or physical properties, such as the temperature or humidity.[60] In this way, everybody participating to the process, enhances its own responsibility and knowledge of the complexity and high interdisciplinarity of scientific "problems". "Ariapesa" is an example of "bottom-up citizen science" promoted by a network of free associations of citizens in Bologna (Italy) to monitor nitrogen oxides in the air near the schools through the installation of hundreds of passive samplers. These samplers have been, and will be, analyzed by specialized laboratories and the results compared to the data of three official monitoring stations, giving a punctual map of the pollution all over the school district.[61]

**Table 1.** Example of quiz report available in Kahoot!, based on the "Domande Periodiche" (Periodical Questions) quiz proposed during the "Chemistry Days" at the University of Palermo.[54]

| **QUIZ TITLE** | Periodical Questions |
|---|---|
| Q1: | What is the surname of the scientist who first proposed the periodic table? |
| Correct answer | D. Mendeleev |
| Players correct (%) | 73.3% |
| Question duration (seconds) | 30 seconds |

| ANSWER SUMMARY | | | | |
|---|---|---|---|---|
| Answer options | Mendel | Mandela | Mendeleev | Mandilei |
| Number of answers received | 8 | 0 | 22 | 0 |
| Average time taken to answer (seconds) | 8.39 | | 6.77 | |

Therefore we believe that, upon appropriate study and definition of shared procedures and metrics to assess the correctness of the information provided, Chemistry should embrace these ways of digital communication and Open Learning.

## CONCLUSIONS

Chemistry, the central science, is often perceived by the general public as "distant from everyday life" and "too abstract". The reasons are manifold and partially addressed herein, however, it is clear that too traditional and content-focused teaching and learning approaches represent an important issue, which may justify the public attitude towards Science and Chemistry, in particular.

In the current digital age, Open Science and, more specifically, Open Learning, offers new paradigms and tools to establish a synergic interaction among science, digital technology, and Society worldwide.

Although the ambitious aim of creating a comprehensive list was beyond our scope, in the present manuscript we reported on successful examples of Open Chemistry, hands-on laboratories during science festivals, and alternative teaching activities based on new media and on the gamification of Chemistry. Some of these activities were developed by us under the umbrella of the "*Diffusione della Cultura Chimica*

– *Società Chimica Italiana*“ (Dissemination of Chemical Culture - Italian Chemical Society) activities, others in the broader framework of the EU mission and vision on communication, dissemination and public engagement.

Moving from the “deficit” to the “dialogue” model of public attitudes towards science, we believe that such new way of promoting interaction between Science and Society holds the promise of triggering general public curiosity and fostering trust in the essential role of Chemistry in our Society.

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# Energy Transfer in Heterogeneous Photocatalysis

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**Abstract.** Electron transfer reactions constitute one of the main pillars of chemistry and numerous examples can be found in nature and in technological applications. Energy transfer induced reactions are more elusive but equally important in phenomena related with natural photosynthesis and in general when light-matter interactions are relevant.

Heterogeneous photocatalysis is generally considered based on electron transfer reactions. In fact, absorption of photons of suitable energy induces formation of photogenerated charges (electron and holes) which in turn initiate redox reactions through interfacial electron transfer to (or from) surface species. However, rare examples of photocatalytic reactions induced by prevailing energy transfer have been recently reported in literature. Investigation in this field may be still defined at a nascent level, and the mechanistic aspects of energy transfer, widely investigated in photochemistry of homogeneous or colloidal systems should be clarified in heterogeneous photocatalysis.

In the manuscript the basic principles of energy transfer will be presented along with some known examples. These concepts will be inferred in the field of heterogeneous photocatalysis, by considering the excited solid semiconductor as the energy donor. Some rare examples of energy transfer induced heterogeneous photocatalytic reactions will be presented along with some tentative mechanistic hypotheses.

**Keywords**. Energy transfer; Heterogeneous photocatalysis; Green chemistry.

## 1. INTRODUCTION

Processes based on energy transfer are nowadays of great actuality. Even if the theoretical description of these phenomena has been clarified last century,[1,2] these basic processes find application in innovative technologies connecting chemistry, biology and physics in interdisciplinary approaches. For instance, techniques based on energy transfer processes have been used to monitor DNA hybridization and sequencing, protein conformation, enzyme activity, and cellular dynamics.[3-5] Other applications concern photonic logic gates[6,7] and energy harvesting.[8,9] The reason for this widespread interest in energy transfer based technologies lies on the extremely high sensitivity to conformational changes in the distance and orientation between energy donors and acceptors. The distance changes observable in this way range from 0.5 to 10 nm so, for this reason, energy transfer based techniques are also referred to as "molecular rulers".[10] Moreover, energy transfer mechanisms have been found to be fundamental for the capture and transmission of light in natural photosynthesis.[11] In fact, photosynthetic organisms use specialized complexes which are able to transfer the captured light energy through an efficiently distributed hierarchy of proteins. This energetic cascade efficiently proceeding in precise time and distance scales, eventually reaches the reaction centres where solar energy is fixed into chemical bonds.

The energy transfer process[12] can be summarized through Eq. 1:

$$D^* + A \rightarrow D + A^* \qquad (1)$$

in which the excited donor ($D^*$) is quenched to its ground state (D) and the released energy is absorbed by an acceptor (A) which in turn is promoted to its excited state ($A^*$).

The simplest energy transfer mechanism is radiative and is known with the name of "trivial". In this case, the emission spectrum of $^*D$ must overlap the absorption spectrum of A in order to make possible the absorption of the photon emitted by $D^*$ by the acceptor A. This process depends on the extent of overlapping of the spectra, on the emission efficiency of $D^*$ (i.e. its quantum yield of emission) and on the concentration of A in the path of photons emitted by $D^*$.

Energy transfer can also occur non-radiatively through Förster or Dexter mechanisms. Förster resonance energy transfer (FRET) occurs from a fluorescent donor to a lower energy acceptor via long-range dipole-dipole interactions. Therefore, FRET mechanism is favoured at a specific geometric orientation and it is highly sensitive to donor-acceptor distances.

The efficiency (E) of FRET can be described by Eq. 2:

$$E = \frac{R_0^6}{R_0^6 + R^6} \qquad (2)$$

where R is the distance between donor and acceptor, and $R_0$, typical for each donor-acceptor couple, is the distance at which the efficiency decreases of 50% (Forster distance). The FRET efficiency can be also expressed in terms of life time (τ) of the donor or of the fluorescence intensity (F) according to Eq. 3:

$$E = 1 - \frac{\tau_{DA}}{\tau_D} = 1 - \frac{F_{DA}}{F_D} \qquad (3)$$

where the subscripts D and DA refer to as the donor and the donor in the presence of the acceptor, respectively. According to Eq. 3, the decrease of the lifetime (or of the fluorescence intensity) of the donor in the presence of an acceptor indicates the existence of FRET.

Finally, the rate ($k_t$) of FRET is described by Eq. 4:

$$k_t = \frac{1}{\tau_D}\left(\frac{R_0^6}{R^6}\right) \qquad (4)$$

FRET mechanism requires a large overlapping between donor emission and acceptor absorption spectra. Energy transfer can also proceed through a "collision" mechanism which is often referred to as "Dexter" mechanism. In other words, the orbitals of the excited donor and of the acceptor in its ground state can overlap giving rise to a double electron transfer which does not modify the total charge of the system, but only its electronic configuration. In this case, the initial steps of the interaction are the same giving rise to electron transfer, but the system evolves differently along with the reaction coordinate and no net charge separation is obtained.

The rate (k) of Dexter energy transfer can be described by Eq. 5:

$$k = KJ\exp\left(-\frac{2R}{L}\right) \qquad (5)$$

where K is a constant related to the specific donor-acceptor couple, J is the normalized spectral overlap integral, R is the distance between donor and acceptor relative to their radii of van der Waals (L).

By comparing Eqs. 4 and 5 it is evident that the rate of energy transfer decreases with increasing R but with different dependence laws. In particular, unlike FRET, Dexter energy transfer becomes negligible when the distance between donor and acceptor increases of few Angstroms. This is quite obvious by considering that Dexter mechanism requires orbital (not only spectral) overlap.

Any fluorescent species such as organic dyes, fluorescent proteins, or nanoparticles can be potentially an energy donor.[13] In particular, semiconductor nanoparticles of few nanometres (quantum dots) have been deeply investigated due to their excellent photo-physical features, stability and versatility.[14-16] However, the donor behaviour of larger semiconductor nanoparticles in energy transfer processes is poorly understood as discussed throughout the text. Demonstrating and opportunely exploiting the presence of energy transfer mechanisms in heterogeneous systems is relevant, for instance, in the fields of photocatalysis and photoelectrocatalysis. These applications are generally based on electron transfer processes occurring on the surface of irradiated semiconductor nanoparticles suspended in a reacting medium or immobilized onto a support.[17,18] Both technologies can be performed in mild conditions of temperature and pressure, with water as the solvent, solar light as the driving force, and by using cheap, abundant and robust semiconductor nanoparticles. These technologies found traditional application in the field of environmental remediation for both water and gaseous effluents.[19] However, applications for the synthesis of high value added compounds are gaining increasing attention due to the appealing features of these processes in terms of conversions, selectivity and sustainability.[20] The product distribution of this traditionally "electron transfer driven" processes can be significantly different when energy transfer processes become the prevailing mechanisms. For these reasons, understanding these mechanisms in heterogeneous photocatalytic systems and developing the technological tools to control and switch them from electron to energy transfer driven processes is highly desired and could open the route to unexplored and exciting novel organic syntheses as green alternative to the traditional ones.

## 2. ELECTRON AND ENERGY TRANSFER IN HETEROGENEOUS PHOTOCATALYSIS

Charge recombination is generally seen as detrimental in photocatalytic reactions as the absorbed energy does not induce interfacial electron transfer but is radiatively or not radiatively emitted. This energy could be in principle transferred to other species in the reacting mixture similarly to colloidal or homogeneous systems. However, even if the formal similarity with energy transfer processes in homogeneous systems is plausible, in heterogeneous systems such as photocatalytic suspensions, it is often difficult to discriminate between electron and energy transfer, mainly due to the presence of solid particles. First of all, light scattering phenomena limit the use of spectroscopic techniques and the consequent achievement of the parameters required for a rigorous characterization of the energy transfer process. For these reasons, up to now energy transfer mechanisms have been highlighted indirectly by considering the product distribution of particular (and rare) reactions. The radiant field distribution in an irradiated slurry suspension is intrinsically not homogeneous and depends on features of the light absorbing species, reactor geometry and configuration, type of radiation and physico-chemical and optic characteristics of the photocatalyst.[21] Indeed, unlike reactants which can be mechanically mixed within the system, photons do not possess mass and their "concentration" decreases with the distance from the radiation source.[22] In these systems it is challenging to retrieve the local value of the rate of photon absorption (RPA) which in turn determines the intrinsic reaction rate.[23] In fact, only the average value of RPA is experimentally accessible while the local one, describing the intrinsic kinetics, i.e. the events occurring at a molecular level not depending on mass and energy transport phenomena, can be retrieved rigorously only by the laborious and time demanding solution of the radiation transfer equation (RTE) by means of numerical methods. Monte Carlo simulations[24] and discrete ordinate methods (DOM) are usually used.[25] This problem has been recently approached by demonstrating that the average values satisfactorily approximate the local ones at sufficiently low optical thickness of the suspension.[23] However, even if RPA could be approximatively retrieved, it is impossible to attribute it to the sole energy transfer events because the macroscopic chemical transformation observed in a photocatalytic reactor is the result of various processes differently interacting in a complex way. Only in few cases it has been possible to unequivocally attribute the formation of an intermediate product to energy transfer mechanisms. As a matter of fact, these cases are rare because the product distribution of electron and energy transfer reactions is often similar. Moreover, even if specific energy transfer derived products could be produced, they must be selectively obtained. This is not trivial, as the hydroxyl radicals photocatalytically produced oxidize almost any organic species with only few exception, and the selective formation of a specific compound is the result of the complex interaction between light, reactants, products, and the irradiated surface of the photocatalyst. Even if the specific compound is selectively obtained, consecutive reactions and adsorption phenomena could mask the identification of the prevailing mechanism. For these reasons, energy transfer mechanisms in heterogeneous photocatalysis have been often vaguely invoked but up to now never directly evidenced. The extent and the nature of the energy transfer processes, deeply clarified in the photochemistry of homogeneous systems, need to be investigated in heterogeneous photocatalysis.

In principle it is possible to hypothesize that the energy transfer mechanisms occurring in homogeneous systems also hold when an energy acceptor locally interact with the excited semiconductor acting as the energy donor. Only some mechanistic details for the formation of singlet oxygen in heterogeneous photocatalysis have been tentatively proposed while less is known when more complex systems are under investigation.[26]

Upon absorption of a photon of suitable energy, an electron ($e^-_{CB}$) and a hole ($h^+_{VB}$) are localized respectively in the conduction and valence band of a semiconductor (SC) according to Eq. 6:[27]

$$SC + h\nu \rightarrow SC^*(e^-_{CB}, h^+_{VB}) \qquad (6)$$

The photogenerated charges migrate to the surface of the semiconductor where they undergo interfacial electron transfer (Eq. 7). In fact, they can reduce or oxidise electron donors (D) or acceptors (A) to the corresponding radical cation ($D^{+\cdot}$) and anion ($A^{-\cdot}$):

$$SC^*(e^-_{CB}, h^+_{VB}) + A + D \rightarrow SC + A^{-\cdot} + D^{+\cdot} \qquad (7)$$

The interfacial electron transfer is thermodynamically feasible if the redox potentials of the couples $A/A^{-\cdot}$ and $D^{+\cdot}/D$ lie within those of the photogenerated charges. However, kinetic limitations or the absence of suitable A and D species in the reacting medium can favour quenching of SC* and, possibly, consequent energy transfer to a generic species B (Eq. 8):

$$SC^*(e^-_{CB}, h^+_{VB}) + B \rightarrow SC + B^* \qquad (8)$$

It is worth to note that the difference between the redox potentials of the SC bands and those of D and A species is the driving force of electron transfer while the downhill character of the process in terms of energy ($E(SC^*) > E(B^*)$) mainly determines the rate of energy transfer. Moreover, while the electron transfer process creates a large charge re-distribution by generating charged species ($A^{-\cdot}$ and $D^{+\cdot}$), energy transfer generates a neutral excited state (B*). As a consequence, for instance the polarity of the solvent affects more the electron than the energy transfer processes. The quenching of the excited semiconductor can occur radiatively by emission of a photon. In this case the energy transfer to the species B occurs by absorption of the emitted photon similarly to the trivial mechanism expressed in homogeneous systems. This process is summarized in Eqs. 9-10 and in Figure 1:

$$SC^*(e^-_{CB}, h^+_{VB}) \rightarrow SC + h\nu \qquad (9)$$

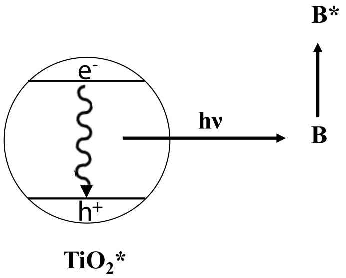

**Figure 1.** Trivial energy transfer mechanism.

$$B + h\nu \rightarrow B^* \qquad (10)$$

This mechanism does not require electronic interaction or even contact between the irradiated semiconductor and the energy acceptor. The efficiency of this type of energy transfer does not depend on the distance between B and the surface of the semiconductor, but mainly on its concentration in the suspension. In fact, at higher B concentrations it increases the number of B molecules in the path of the emitted photons.

Other factors influencing the efficiency of the trivial mechanism are the charge recombination rate and the probability to emit photons rather than heat. Moreover, it is required that the emission spectrum of the semiconductor and the absorption spectrum of B overlap in order to avoid mismatch between the excited semiconductor and the acceptor.

Unlike the trivial mechanism, Förster and Dexter energy transfer are radiationless processes and depend on the distance of the acceptor from the semiconductor (even if with different dependence laws, see Eqs. 4-5).

No electron exchange between acceptor and donor occurs when Förster mechanism takes place (Figure 2). Indeed, the oscillating electric field locally produced by the separated charges behaves as a virtual photon which excites the acceptor through dipole-dipole interactions. Notably, the oscillating field can be generated both by charges localized in the valence and conduction bands upon band to band transitions, or within the conduction band by vibrational states transitions.

On the other hand, Dexter energy transfer mechanism occurs when simultaneously two electrons move in opposite directions (from donor to acceptor and viceversa) without net charge exchange (Figure 3).

It is generally accepted that in heterogeneous photocatalysis electronic interaction occurs through surface adsorption of a substrate, which generally gives rise to surface metal coordination compounds. Adsorption perturbates the electronic structure of both semiconductor and adsorbate at different extents.[28] This situation is

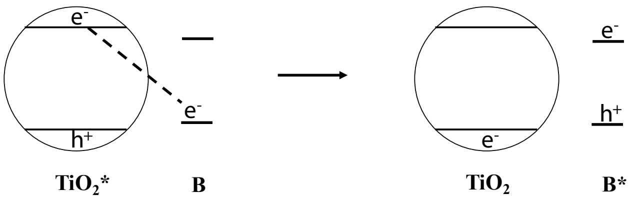

**Figure 2.** Förster energy transfer mechanism.

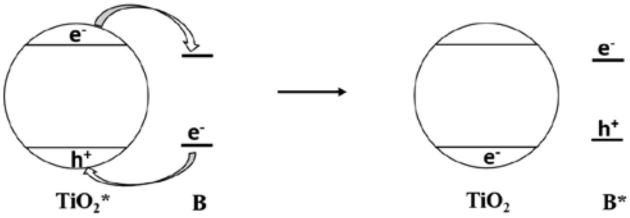

**Figure 3.** Dexter energy transfer mechanism.

similar to what occurs in Dexter processes at the initial stage of interaction but, as below detailed, generally it results in interfacial electron transfer.

Strong electronic coupling between adsorbate and semiconductors generates new energy levels.[29] Combination of the HOMO level of the adsorbate with conduction band surface states creates a surface hybrid HOMO-LUMO system between the adsorbate and the semiconductor which can extend deeply into the semiconductor due to its band structure. The resulting electronic system is generally characterized by novel ligand to metal electronic transitions, usually in the visible light region, which can be classified as optical electron transfer (OET). In this case, neither the semiconductor nor the adsorbate alone are able to absorb visible light, while the resulting charge transfer complex does. Various organic and some inorganic compounds present this behaviour when adsorbed onto a semiconductor such as aromatic 1,2 diols, some lignin components and $SO_2$. The extent of this electronic interaction is evident when considering the effects of the adsorption of these compounds onto colloidal semiconductor nanoparticles (ca. 3 nm sized). In fact, in this cases the electronic alteration of the band structure is extended to the whole particle and a significant red shift of the band gap is obtained rather than novel absorption bands. Notably, similar behaviour is reported also for other strongly interacting electronic systems such as solid solutions of semiconductors.[30] Weaker electronic coupling generally favours electron transfer from the adsorbate to the semiconductor or, in rare cases, viceversa. This mechanism, also known as photoinduced electron transfer (PET), usually takes place when chromophore species such as dyes are adsorbed on a semiconductor.[31] Visible light radiation absorption promotes the dye to its excited state which in turn injects an electron in the conduction band of the semiconductor. This weak electronic coupling determines high electron transfer efficiency and low charge recombination and, therefore, these systems are often used in dye sensitized solar cells. Notably, these considerations justify the necessity to avoid the use of dyes as model compounds when one needs to estimate the visible light photocatalytic efficiency of novel semiconductors. In fact, the dye degradation rate expresses the efficiency of electron injection from the excited dye to the conduction band of the semiconductor rather than the activity of the semiconductor.

It is generally accepted that the above reported electronic interactions favour optical or photoinduced electron transfer. On the other hand, as far as the energy transfer in photocatalysis is concerned, indirect observations suggest that energy transfer is prevailing when the surface of the semiconductor is grafted with species which block or substitute the surface hydroxyl groups, as in the examples reported in the next Section. Therefore, it seems that the direct contact between semiconductor and substrate favours electron transfer, while a mediated contact or a certain distance between them could favour energy transfer. For this reason, it seems plausible that some energy transfer processes observed by blocking the surface of the semiconductor could be of trivial or Förster nature.

Even if, up to now, the few examples of energy transfer driven photocatalytic reactions reported do not allow to further discriminate between them, it is possible to conclude that surface grafting can be proposed as a tool to switch between energy and electron transfer processes.

Hydroxyl groups mainly origin from dissociative adsorption of water at the surface of the semiconductor.[32] They determine the acidity and basicity of the surface, are responsible for the hydrophilicity (and superhydrophilicity) of the surface and influence the water dynamics and the competition between different substrates, greatly affecting the selectivity of photocatalytic reactions. In some cases, the hydroxylation density favours the photocatalytic activity even if not all of the surface hydroxyl groups are able to generate hydroxyl radicals. However, for the purpose of this paper, it is worth to stress the role of hydroxyl radicals in determining the electronic features of the semiconductor. First of all, protonation or deprotonation of hydroxyl groups changes the charge of the surface. Therefore, pH changes can shift the potentials of the valence and conduction band and influence the redox ability of the irradiated semiconductor. Moreover, hydroxyl groups can act as traps for the photogenerated charges which thus prolong their life time and facilitate interfacial electron transfer. Moreover, as mentioned above, they act as anchoring sites for organic species and mediate the electronic modifications induced by the interaction. As a consequence, blocking these sites may favour charge recombination thus reducing the probability of efficient charge transfer.[26]

## 3. EXAMPLES OF ENERGY TRANSFER DRIVEN PHOTOCATALYTIC REACTIONS

Some significant examples of energy transfer driven processes have been obtained in plasmonic photocatalytic composites used as sensors or as oxygen getters, but only rarely energy transfer driven processes have been invoked in classical heterogeneous photocatalysis for degradation or synthetic applications.

One of the first examples of energy transfer process in heterogeneous photocatalysis has been reported by Wang et al.[33] Authors hypothesized, without providing conclusive demonstration, that an array of vicinal $TiO_2$ nanoparticles could enable energy transfer through an antenna mechanism similar to the natural photosynthetic process of the same name (Figure 4).

An interesting case of photocatalytic mechanism which can be possibly interpreted as an energy transfer process is the hole induced oxidation of alcohols.[34] This reaction generally occurs through abstraction of a hydrogen atom from the α position, giving rise to α-hydroxyalkyl radicals (Eq. 11):

$$R{-}CH_2{-}OH + h^+ \rightarrow R{-}\dot{C}H{-}OH + H^+ \qquad (11)$$

These radicals are generally powerful reducing species which can then inject an electron into the conduction band of the semiconductor according to a photoelectrochemical process often referred to as "current doubling effect" which eventually produce the carbonyl compound.[35] This example is paradigmatic for at least two reasons. Firstly, by considering that the spatial charge separation of the photogenerated electrons and holes is only some Angstroms across the surface of the excited semiconductor, it is highly probable that the current doubling effect occurs in a concerted way rather than as a two-steps process. In this case it could be tentatively seen as a Dexter energy transfer. Secondly, the sole presence of the carbonyl product is not an evidence of an energy transfer mechanism, as the same product can be obtained also through other mechanisms. In fact, evidences of current doubling effects have been obtained by photocurrent measurement rather than by simple photocatalytic experiments. This example highlights the difficulties faced in trying to evidence energy transfer mechanisms in photocatalytic reactions.

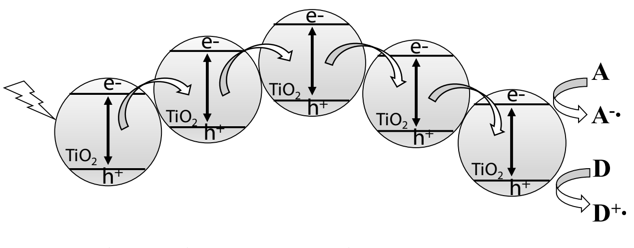

**Figure 4.** Photocatalytic antenna mechanism.

Direct or indirect detection of singlet oxygen in aqueous photocatalytic suspensions is an indirect demonstration of the existence of energy transfer triggered process in heterogeneous photocatalysis. Molecular oxygen exists in its ground state as a triplet. Two excited states of molecular oxygen can be obtained upon excitation. The energy of these two singlet states, denoted as $^1\Sigma_g^+$ and $^1\Delta_g$ lie 158 and 95 kJ·mol$^{-1}$ above the energy of the ground state, respectively. The $^1\Delta_g$ state, commonly denoted as $^1O_2$, is the more stable of the two excited states and is enough long living to induce chemical transformation under mild conditions.

Formation of singlet oxygen in the presence of irradiated $TiO_2$ as the semiconductor has been explained by Nosaka et al.[36] in terms of double electron transfer in opposite direction. In fact, molecular oxygen can be first reduced by a photogenerated electron at the surface of $TiO_2$ to superoxide anion radical which in turn can be oxidized by a photogenerated hole giving rise to singlet oxygen. It is evident that the result of this mechanism is a neutral species (singlet oxygen) and no net charge exchange occurs. To the best of our knowledge, there are no clear evidences that this double electron transfer occurs in a consecutive or in a concerted way. In the second case, similarly to the current doubling effect mentioned above, the formation of singlet oxygen could resemble a Dexter type energy transfer mechanism.

Other authors hypothesized that trivial mechanism could be responsible for the formation of singlet oxygen, i.e. that the radiative emission occurring upon charge recombination in the semiconductor could afford triplet to singlet excitation of molecular oxygen.[37] However, Daimon et al. pointed out the energetic mismatch between the band gap of the considered semiconductor ($TiO_2$) and the energy difference between triplet and singlet oxygen states.[38] By taking into account this observation, recently Macyk et al.[39] proposed the formation of singlet oxygen in the presence of surface modified

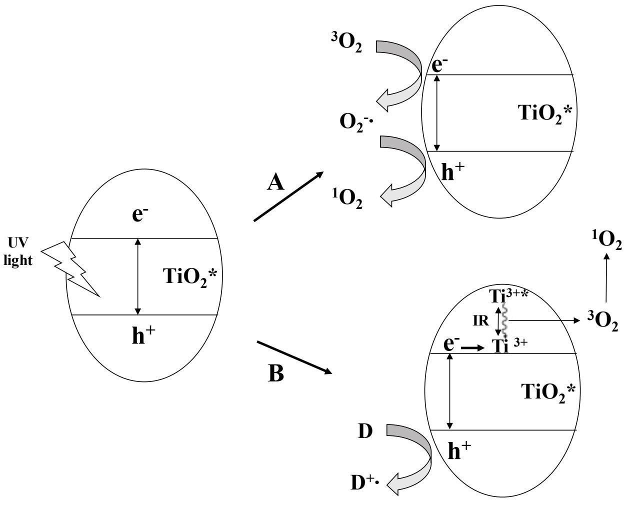

**Figure 5.** Mechanisms of singlet oxygen formation. A: Nosaka mechanism; B: Macyk mechanism. Notably, the $TiO_2$ surface has been functionalized in the experiments carried out by Macyk et al. [39]

$TiO_2$, through energy transfer from excited $Ti^{3+}$ species to molecular oxygen. In this case the energetic differences between the states in the donor (semiconductor) and acceptor (molecular $O_2$) are compatible. The semiconductor quenching responsible for the transfer, in this case, is an intra-band transition (within the conduction band) rather than band to band recombination (Figure 5). Unfortunately, the nature of this energy transfer has not been highlighted.

Also in this case surface modifications performed by substituting hydroxyl with fluoride groups or by anchoring organosilanes, organic molecules or platinum complexes are reported to enhance the production of singlet oxygen. For instance, Janczyk et al.[37] observed efficient photocatalytic degradation of cyanuric acid only in the presence of surface modified $TiO_2$. In fact, cyanuric acid is one of the few compounds which cannot be photocatalytically degraded by bare $TiO_2$, due to its stability even in the presence of hydroxyl radicals, superoxide anions and peroxides, but it can be oxidized in the presence of singlet oxygen.

These reports elegantly demonstrate that (i) singlet oxygen can be produced in aqueous irradiated suspensions of $TiO_2$, and that (ii) modification of the surface of $TiO_2$ promotes the production of singlet oxygen.

A similar indirect demonstration of significant singlet oxygen formation in the presence of surface modified $TiO_2$ has been recently reported by Ciriminna et al. [40,41] In this case a synthetic approach has been used. The considered reaction is the epoxidation of limonene (see Figure 6).

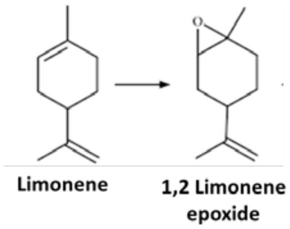

**Figure 6.** Limonene epoxidation.

This natural terpene is gaining increasing attention because it can be used as a raw material for the production of a promising biopolymer, i.e. polylimonene carbonate (PLC). PLC is biodegradable, presents high thermal resistance (transition temperature up to 180°C), high transparency, and exceptional gas permeation ability. These features make PLC a green alternative to the petrochemical derived polycarbonates with applications in the field of breathing glasses and food safe plastics. Moreover, the presence of an exocyclic C=C double bond, easy to functionalize, makes the properties of PLC extremely tunable for innovative applications such as sea water soluble polymers and antibacterial polymers. The bottle neck of the PLC production is its starting material, i.e. limonene epoxide (LE). LE is obtained industrially from limonene in low yields and harsh operative conditions (Prileshayew reaction). Recently, limonene epoxide has been obtained with high conversion and selectivity (up to 90%) in the presence of surface modified commercial $TiO_2$ (Evonik) under simulated solar light and in acetonitrile as the solvent. While OH radicals formed in the presence of bare $TiO_2$ mainly induced overoxidation of limonene, alkyl silane modification of $TiO_2$ favoured formation of singlet oxygen which selectively oxidizes limonene to 1,2 limonene epoxide.

Another example of energy transfer driven process is the photocatalytic isomerization of caffeic acid in aqueous $TiO_2$ suspensions and under nitrogen atmosphere[42] (Figure 7).

UV irradiation of aqueous solutions of *trans*-caffeic acid in the absence of the semiconductor induces photochemical formation of the *cis* isomer until a pho-

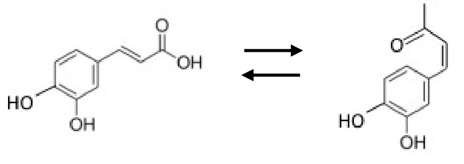

**Figure 7.** Isomerization of caffeic acid.

tostationary *cis/trans* ratio is achieved. In the presence of $TiO_2$ a higher *cis/trans* ratio has been observed. This finding suggests that photocatalysis contributes to isomerization along with the photochemical process. Various tests have been performed in order to highlight this result. Photocatalytic degradation of caffeic acid is suppressed being the reaction carried out under nitrogen atmosphere. This factor supports the hypothesis of energy transfer due to the high recombination probability in deoxygenated suspensions. Moreover, in the presence of 2-propanol as the hole scavenger, isomerization was totally inhibited and again surface modification of $TiO_2$ further enhanced the *cis/trans* ratio.

## 4. CONCLUSION AND PERSPECTIVES

Heterogeneous photocatalysis has been generally considered as the result of electron transfer reactions mainly occurring at the surface of the irradiated semiconductor. The possibility of addressing the product distribution of photocatalytic reactions and of obtaining selectively some reaction intermediates as high value added compounds, recently moved the attention of the scientific community towards photocatalytic syntheses rather than photocatalytic degradation. As a matter of fact, after ca. 50 years of scientific investigations on photocatalytic water purification, the gap between laboratory solutions and the needs of the water purification industry is evident. A change of direction is required in this field. It makes sense to use photocatalysis, possibly coupled with other advanced oxidation processes, to get rid of compounds harmful at low concentrations but only as a final treatment, after the application of technologies capable to efficiently treat high volumes of effluents. Robust and reusable photocatalysts should be used rather than elegant and complex composites and applicative and engineering issues must be faced rather than basic research. The situation is different when considering photocatalysis as a green alternative to traditional organic synthesis methods. In this case basic research is still needed to develop tools to control and address the selectivity of the process and to propose novel and sustainable synthetic solutions. From the few examples summarized hereby it is possible to conclude that when the substrate electronically interacts with the surface of the semiconductor, electron transfer is generally the prevailing process, even if Dexter-like double electron transfer processes cannot be excluded. On the other hand, trivial or Forster energy transfer processes likely occur at the surface of modified semiconductors where orbital overlapping is less probable. These preliminary results, however, require further efforts to understand the energy transfer processes occurring in irradiated photocatalytic systems. In our opinion this knowledge will induce the development of tools allowing to efficiently switch from electron to energy transfer reactions and will open novel possibilities especially in the field of the green photocatalytic synthesis of high value compounds.

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