This is an author version of the contribution published on:

[Ultrasonic Sonochemistry. 2015, 25, 8-16]

The definitive version is available at:
[http://www.journals.elsevier.com/ultrasonics-sonochemistry/]
Enabling Technologies Built on a Sonochemical Platform: Challenges and Opportunities

Pedro Cintas\textsuperscript{a}, Silvia Tagliapietra\textsuperscript{b}, Marina Caporaso\textsuperscript{b}, Silvia Tabasso\textsuperscript{c}, Giancarlo Cravotto\textsuperscript{b,*}

\textsuperscript{a}Departamento de Química Orgánica e Inorgánica, Facultad de Ciencias-UEX, Avda. de Elvas s/n, E-06006 Badajoz, Spain.
\textsuperscript{b}Dipartimento di Scienza e Tecnologia del Farmaco and Interdepartmental Centre “Nanostructured Interfaces and Surfaces - NIS, University of Turin, Via P. Giuria 9, 10125 Turin, Italy.
\textsuperscript{c}Dipartimento di Chimica, University of Turin, Via P. Giuria 7, 10125 Turin, Italy.

Abstract
Scientific and technological progress now occurs at the interface between two or more scientific and technical disciplines while chemistry is intertwined with almost all scientific domains. Complementary and synergistic effects have been found in the overlay between sonochemistry and other enabling technologies such as mechanochemistry, microwave chemistry and flow-chemistry. Although their nature and effects are intrinsically different, these techniques share the ability to significantly activate most chemical processes and peculiar phenomena. These studies offer a comprehensive overview of sonochemistry, provide a better understanding of correlated phenomena (mechanochemical effects, hot spots etc.), and pave the way for emerging applications which unite hybrid reactors.
1. Introduction

Chemical industries and laboratories are heavily involved in the development of mild, simple, environmentally friendly and inexpensive catalytic processes that adhere to the principles of green chemistry and process intensification, as well as fulfilling competitive production requirements. There is currently a huge gap between classic production processes and the new green integrated technology based protocols which aim for higher efficiency and sustainability. In spite of chemistry's multidisciplinary interactions, chemists are often extremely conservative when designing their experimental protocols. Nevertheless, the last few years have seen chemists and chemical engineers from various research fields meet under the ample umbrella of sustainability and share experiences and backgrounds. It is in this context that sonochemistry, whose effects arise from the action of ultrasound waves in liquids, has branched out into techniques like the closely related hydrodynamic cavitation (HC), microwave irradiation (MW), mechanochemical activation and flow chemistry (FC) in both meso- and microfluidic reactors. The purpose of this concise review is to draw attention to the above-mentioned combinations, their practical operational applications and reduced environmental and economical impact. The concept of synergy, i.e. the fact that the benefits of the hybrid protocol exceed those of each technique alone, has been well documented. However, the literature also deserves a more a critical assessment which highlights pros and cons alike. We believe that in doing so the discipline of non-conventional technologies will be recognized still further as a powerful ally to green chemistry and beyond.

2. Ultrasound and microwave irradiation

While popular wisdom simply associates MW with superior heating and US with efficient agitation, these techniques are capable of doing so much more and this potential provides additional impulse to their expansion in synthesis and processing [1]. Acoustic and MW fields can be coupled in a variety of forms which can provide synergy, but also harness particular properties. An overview of such opportunities is shown in Figure 1. It may not be immediately obvious how these physical fields work together as they show different characteristics; MW is electromagnetic radiation while ultrasound lacks quantum character. Neither of them interacts with matter at a molecular level as reflected by their wavelengths and low energies. Nevertheless, both cavitation and dielectric heating account for molecular excitation by creating microzones in which local heating becomes densely concentrated.
Figure 1. Ultrasound (US) and microwaves (MW) interplay.

Not all sonochemistry practitioners will be aware that acoustic waves can be generated in viscoelastic media by pulsed MW, which means that various different resonance frequencies are obtained when piezoelectric bars are excited electrically or by MW irradiation [2,3]. This is a thermoelastic mechanism of acoustic wave generation that can be harnessed in the non-destructive evaluation of piezoelectric samples. As a proof of concept, a composite plate containing oriented graphite fibres was subjected to MW-excited irradiation (9.41 GHz) which gave rise to US waves with frequencies over 100 kHz [4]. It is interesting to note that as the polarization of the MW beam is rotated (from normal to parallel to the continuous fibers), the absorbed MW energy decreases significantly, thereby decreasing concomitantly the amplitude of the resulting acoustic wave. The major portion of the MW energy is reflected back by the graphite fibers. As mentioned, non-destructive inspection may benefit from this concept, although only laminates having graphite fibers concentrated in or near a single axis will be sensitive to this effect. Applications to other carbonaceous and dielectric composites can be surmised.

Likewise and yet disconnected from chemical matters, MW and US can be coupled in a sequential fashion in therapeutic medicine (Figure 1). MW irradiation constitutes an important ablation technique against some carcinomas along with laser ablation and high-intensity focused ultrasound (HIFU). In this therapy, a MW antenna is percutaneously inserted into the tumour under the guidance of US waves and heats the zone until coagulation occurs. The process requires in-situ monitoring which is usually accomplished by magnetic resonance imaging (MRI). Its high resolution is certainly
an advantage; however, MRI is costly and gives poor real-time data acquisition. These limitations can be overcome by the use of ultrasonic imaging that possesses suitable human-body penetrability and enables local temperature monitoring [5].

A substantial body of research into the combined use of MW and US has been devoted to enhancing chemical reactivity as well as to improving chemical processing and separation. Although pioneering works in the field threw up various technical and safety considerations in combining US and MW irradiation, the last decade has seen their coupling efficiently performed on lab and pilot scales [6-10]. MW and US can be employed in simultaneous and sequential modes (Fig. 2), which can either involve the use of loop reactors with two separate compartments or typical two-step treatments (presonication and MW-assisted reaction).

Figure 2. Hybrid loop reactor with two different horn set up: A) Simultaneous US/MW irradiation, B) sequential US/MW irradiation in separate vessels.

Loop reactors and flow systems are particularly attractive for selective activations and show promise as automation may cause batch MW- or US-based chemistries to develop into cleaner and more efficient continuous processes (vide infra). As mentioned above, enhanced chemical effects have been observed when dielectric heating is associated with the large amount of energy released in cavitational collapse, causing particle fragmentation (especially in heterogeneous transformations) and molecular excitation.

The use of hybrid US/MW irradiation in plant molecule extraction is truly remarkable. Plants are an invaluable source of bioactive substances for the pharmaceutical and nutraceutical industries as well as being important in the preparation of perfumes and cosmetics. This combination is often superior
to ultrasound- and MW-only assisted extractions (UAE and MAE, respectively) and leads to higher yields in shorter reaction times [8,11]. Prolonged sonication can become detrimental and decomposition is a potential, undesirable side effect, particularly with sensitive molecules.

Most synthetic uses of the US/MW marriage are found in classical organic reactions and in metal-assisted catalytic reactions, in particular. Applicability has so far been limited to a few venerable reactions such as the Suzuki, Heck or click reactions and has proven to be indispensable in modern organic synthesis. This field would clearly benefit from further exploration into the use of combined irradiation, but will also require precise reaction set-up design which would be able to convert the aforementioned physical effects into solid results in terms of reactivity and thereby provide satisfactory rationales. Early studies, such as the hydrazinolysis of esters in solventless conditions for example [12], were conducted in simple, home-made devices by inserting a detachable horn into a modified domestic oven. Despite this same procedure furnishing both reaction acceleration and high-yielding syntheses [7,8], it can no longer be employed as the use of domestic ovens is strongly discouraged in contemporary studies because of its lack of reproducibility and inaccuracies in power and temperature measurements. Moreover, horn material was not always specified, which may have misled many readers (as hazards may occur when metallic materials are irradiated by MW).

Any combination of MW and US waves should not only elicit caution against potential risks, especially when using MW-absorbing materials, but also accurate bulk temperature control via optical fibre measurements. A hot debate on the existence of specific thermal effects in MW-irradiated reactions is currently intense [13,14]. Flawed conclusions can be reached if a proper estimation of the internal temperature is not achieved. Agitation, in fact, often contributes to temperature homogenization [15]. Regarding the acoustic field, quantification of the intensity delivered into the hybrid reactor using dosimetry methods is likewise compulsory. Newcomers and occasional users may neglect the fact that, even though frequency is not directly related to acoustic energy, higher intensity will be required at higher frequencies for cavitation to occur.

Ragaini et al. have devised a batch reactor which enables simultaneous MW and US irradiation, where MW irradiation (2.45 GHz, 900 W) is delivered into the liquid by a coaxial antenna which is insulated from a titanium horn emitting pulses at 20 kHz (295 W), thus avoiding the formation of sparks or electrical discharge (Figure 3). The authors noted additive and synergistic effects when water or cyclohexane were irradiated. Synergy increased as the US power increased (up to 71% nominal power emission) and, remarkably, cyclohexane was much more efficiently heated under simultaneous irradiation than with US alone; as expected for an apolar molecule, MW alone had no effect [16]. This result suggests that cavitation might still generate polar species (or radicals) from apolar molecules, whose heating will then be enhanced by MW.
A synthetically useful example of sequential irradiation is supplied by the Pd-catalyzed homo- and cross-couplings of boronic acids and aryl halides, which have been carried out in aqueous media using a flow reactor which was thermostated at 45 °C, under combined US (20.5 kHz, 40 W/cm²) and MW (700 W) irradiation and drawing on 10% Pd/C as a cheap catalyst. The expected biaryls were obtained after 1 h-irradiation as the sole products, in higher yields than those achieved under either US or MW used separately [17]. Simultaneous MW/US irradiation has also been applied to another classic Pd-based protocol, the Heck reaction, for which high product yields were obtained using very low ligandless catalyst loads, either Pd(OAc)₂ or Pd/C [18]. In most cases MW heating gave comparable results (although yields were 5-20 percent lower) in somewhat longer times, whereas under conventional heating acceptable yields were only achieved after 18 h (Scheme 1, Table 1).
Scheme 1. Pd-catalyzed Heck reactions producing cis- and trans-stilbenes.

Table 1.2 Cis:trans selectivity (GC analyses) of Heck reactions between 4-iodoanisole and styrene performed under MW and/or US irradiations.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Oil bath (120 °C)</th>
<th>MW (120 °C, 60 W)</th>
<th>MW (50W) / US (40W) (120 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(OAc)$_2$, 0.1 mol%</td>
<td>9 : 57, a 12 h</td>
<td>19 : 78, 1.5 h</td>
<td>9 : 90, 40 min</td>
</tr>
<tr>
<td>Pd/C 2.0 mol%</td>
<td>11 : 80, 20 h</td>
<td>16 : 80, 3 h</td>
<td>19 : 81, 1 h</td>
</tr>
</tbody>
</table>

aIsolated yields

There is little doubt that the Cu-catalyzed azide-alkyne cycloaddition (CuAAC) is the paradigm of click reactions. Its biorthogonality in living processes constitutes an advantage when producing novel bioconjugates and modified drugs. This versatile [3+2] cycloaddition has been successfully performed under simultaneous US/MW irradiation, even using metallic copper powder as catalyst in the place of copper salts [19]. The reaction does not require ligands and reducing agents, and can be applied to sensitive and highly functionalized molecules like cyclodextrins (Scheme 2). In general, this one-pot protocol affords products in higher yields (> 80 percent) and in much shorter times than conventional heating does (6-10 h) [20].
Scheme 2. Click azide-alkyne cycloadditions catalyzed by metallic copper or copper salts, activated by MW and/or US irradiation.

In materials chemistry, a few reports have documented the favourable combination of US and MW for the preparation of nanomaterials [21]. This application is clearly still in its infancy and yet is enormously promising. The preparation of platinum nanoparticles in a heterogeneous solid-liquid system via simultaneous US/MW irradiation leads to excellent homogeneous distribution relative to conventional thermal methods [22]. Analogously, high-purity cadmium sulfide nanostructures (flower-like hexagonal nanopyramids and/or nanoplates) have been obtained in a hybrid reactor [23]. Also worthy of note are recent efforts into the use of MW and US, whether used combined and separately, for the purification and surface functionalization of layered materials such as carbon nanotubes, graphene oxide and graphene itself [24]. US irradiation is now an ideal method for achieving facile liquid-phase exfoliation in a variety of solvents, by virtue of the mechanical forces generated after bubble collapse which disrupt the weak intermolecular interactions present in the above materials. Prolonged sonication also causes superficial oxidation [25], and the process is further enhanced by MW. The use of combined MW/US (the latter operating at 300 kHz) on multi-walled carbon nanotubes triggers extensive oxidation and damage, although the protocol efficiently removes the amorphous external layer [26]. The role of mechanical forces in this context (vide infra) is still
poorly understood. Cavitation control becomes more important than the blind delivery of acoustic power as exfoliation and dispersion are largely dependent on inertial cavitation and not on the stable stages [27].

In some cases, a sequential two-step approach is more suitable for controlled surface derivatization than the combined irradiation, for which optimal conditions can be difficult to achieve. As exemplified in the synthesis of graphite halides, the halogenation step (which first involves the intercalation of the halogen between the graphite layers) is significantly accelerated by MW and, subsequently, the modified material can be easily exfoliated into monolayer graphene in organic solvents under mild sonication (Figure 4) [28]. Conversely, brief sonication can be employed for dispersion and exfoliation prior to chemical functionalization of otherwise MW-absorbing carbonaceous substrates [29]. As mentioned earlier, no special precautions are needed so long as low-frequency US irradiation is maintained only for a few minutes, thereby not affecting the single layers.

![Figure 4](image.png)

**Figure 4.** (a) Schematic representation of the sequential MW-assisted graphite halogenation and subsequent sonication-promoted exfoliation. (b) Photographs of graphite chloride. (c) Graphite chloride dispersion in DMF. (d) Graphite bromide dispersion in DMF. Reproduced with permission from ref. [28]. Copyright 2012 Macmillan Publishers Ltd.

A final application that illustrates the multifaceted and far-reaching scope of the MW/US combination is provided by a rather sophisticated technique termed *sonoplasma*. Here, a stable plasma can be maintained in a liquid hydrocarbon which is exposed to MW (2.45 GHz, 100-200 W) which irradiates a pressurized quartz chamber where acoustic cavitation bubbles are generated by a titanium horn emitting at low ultrasonic frequency [30]. The protocol competes favourably with plasma generated
by chemical vapour deposition, whose stability is problematic. The process is not yet routinely employed; although a recent application in environmental studies deserves attention (Figure 5). The advanced oxidation of perfluorooctanoic acid (ca. 60% degradation) in aqueous media thus takes place after 90 s of plasma irradiation [31].

Figure 5. (a) Schematic representation of a device generating MW discharge plasma with simultaneous acoustic cavitation. (b) Photograph of the experimental set-up. Reproduced with permission from ref. [31]. Copyright 2011 Elsevier B. V.

Sonochemistry and mechanochemistry

The fact that sound, which manifests itself through the action and propagation of pressure waves in elastic media, is essentially mechanical energy is generally overlooked. Mechanical effects can be detected at a wide range of frequencies and intensities, including audible sound. However, appreciable effects at a molecular level will only be detected at ultrasonic frequencies after cavitational collapse, although other parameters (solvent nature, dissolved gases, temperature, or molecular structure) should be given serious consideration. Acoustic cavitation may initiate chemical reactions via excited, short-lived species which are formed inside the bubbles along with post-cavitational mechanical effects that mainly arise from shear forces and shock waves occurring at the bubble-liquid interface. These effects are particularly evident in heterogeneous solid-liquid reactions involving non-volatile reagents and account for cleaning, erosion, dispersion as well as enhanced mass transfer and often modify the reactivity of surfaces and particles. Sonochemical reactivity can therefore be subjected to tribochemical interpretations. Sonication does effectively create tensile forces in liquids that trigger a
given chemical transformation, just like solid-state reactions can be activated under mechanical stress (friction or grinding, for instance). Although some relationships between the disciplines, even in quantitative form, can be established, the complexity of cavitation as a physical phenomenon hampers straightforward parallels. Two important domains, crystallization and polymer chemistry, benefit considerably from the growing interest in applying ultrasonic activation to such scenarios and have been documented in recent review articles [32-36]. The effects associated with sonocrystallization are varied, although there is ample evidence to suggest that ultrasound significantly narrows the metastable zone, thereby favouring nucleation stages. In addition, crystal size distribution becomes more homogeneous, which provides advantages in the preparation of pharmaceutical ingredients in particular. A satisfactory rationale for this, however, is still open to debate but appears to be dependent on the parent structure, among other factors. Thus, sonofragmentation is linked to direct interactions between particles and shock waves in organic crystals, while both interparticle collisions and collisions with the ultrasonic horn or walls, which might be favoured by turbulent flow, have however been dismissed [37]. High-speed photography, which can record calcite sonocrystallization, has ruled out interparticle collisions as well and pointed to the role of cavitation clusters, i.e. bubble nucleation on the inorganic material, as the dominant mechanism [38]. Since molecular orientation during nucleation may also be altered by US irradiation, morphological changes in organic nanocrystals have also been reported [39].

It is now well established that sonication promotes both polymer formation and depolymerization via the mechanical forces released by cavitation collapse which usually involve radical pathways that occur at the bubble interface as large molecules will rarely enter the microbubbles [40]. This brings to mind a certain analogy with polymer mechanochemistry where chain bonds fragment during milling, grinding or shearing leading to “mechanoradicals”, which drive the transformation to completion according to the expected steps of addition and recombination. While ultrasound induced degradation might not be considered particularly useful synthetically, chain scission is not completely random and often occurs at weak bonds and functional groups (mechanophores) that respond preferentially to mechanical stress in a controlled manner. These processes may however be negligible in homogeneous solution for small molecules. Shock waves will affect the mechanophore unit so long as the adjacent fragments undergo substantial deformation. In this sense, the polymer chain functions as molecular tweezers that transmit mechanical energy and thus a threshold molecular weight is critical. A variety of interesting transformations have been achieved when well-designed mechanophores have been properly outfitted with polymer chains, these include; thermally inaccessible isomerizations and cycloreversions, symmetry-forbidden electrocyclic ring openings and the activation of latent catalysts [33-36]. Such processes open the door to novel sonochemically-
responsive mechanical actuators with multiple applications. In an illustrative example; a dioxetane mechanophore inserted into a polymer chain can be selectively cleaved under sonication. Blue luminescence, whose intensity and colour were modified by the presence of energy-transfer acceptors, was then observed from the resulting ketone excited species (Figure 6) [41]. The method is potentially valuable for testing defects or failures in polymeric materials. In a more recent application, Moore and associates have devised a metastable poly(α-phthalaldehyde) material that undergoes ultrasound-induced mechanical depolymerization to the parent monomers via a heterolytic mechanism. Repolymerization was then easily achieved by a chemical initiator, thus mimicking the depolymerization-polymerization cycles that are characteristic of numerous biological processes [42].
Figure 6. Sono-scission of a polymer chain which includes a 1,2-dioxetane mechanophore to form an adamantanonone-excited species that emits light. Luminescence spectra obtained during the mechanical stretching of polymers that contain organic acceptors show different colours and intensities. Reproduced with permission from ref. [41]. Copyright 2012 Macmillan Publishers Ltd.

As briefly noted above, the mechanical effects caused by sonication are highly influenced by the specific parameters of any given sonochemical experiment [33,34,36]. The effect of frequency is probably more difficult to rationalize as it also influences radical production. On the other hand, mechanical effects such as acoustic pressure or acoustic intensity, which are measured by different methods, have been accounted for using various concepts. Mason and co-workers have found additional evidence for mechanical and chemical effects' inverse dependence on ultrasonic frequencies, although power intensity (evaluated using calorimetry) decreases as frequency increases [43]. Tran et al. have reached similar conclusions in a further study where frequency varied from 20 kHz to 1 MHz, but insisted on the use of constant power intensity. On measuring degradation rates and viscosity ratios when polyethylene oxide (in water or benzene solutions) and polystyrene (in benzene only) were irradiated, these authors found that mechanical effects slow down above 100 kHz [44]. These re-assessments are especially valuable as one feels that only a certain accuracy in our knowledge of cavitational effects will allow us to understand how ultrasound exerts mechanical force.

Combined acoustic and hydrodynamic cavitation.

We now move on to the field of sonochemical flow-reactors where the combined use of ultrasonic and hydrodynamic cavitation has been reported [45]. Both types of cavitational reactors have so far found widespread use in the areas of chemical processing, water and effluent treatment, polymer chemistry, solid-liquid extraction, etc. Although appropriate technical set-up design is required to maximise the additive effects of US and HC, Bremner et al. have provided evidence of clear improvements in hydroxyl radical generation at an orifice-transducer distance of 5-10 mm (Fig. 7).
Reproduced with permission from ref. [45]. Copyright 2008 Elsevier.

Water treatment processes usually operate at continuous flow and take advantage of the combination from ultrasonic and hydrodynamic waves with Fenton chemistry [46]. An industrial hybrid HC/US reactor for waste treatment process of coal gasification fly ash has been recently patented [47].

Ultrasound reactors associated with flow micro- meso-fluidic reactors
Sonication (or MW irradiation) aided flow system chemistry has become a prominent method for carrying out chemical transformations in recent years [48]. Sonication has largely been used to generate liquid flow and prevent the deposition of solids [49]. A combination with microreactors is technically feasible and may lead to synergistic results while miniaturization is obviously part of a modern trend which can reduce waste, is suitable for scaling up and often tolerates toxic and expensive reagents as they are employed in very small amounts. Thanks to a huge contact surface and multi-unit loop assembling, cavitation reactors (hydrodynamic systems, high-shear mixers, ultrasonic transducers), which are hybridized with flow micro- or meso-fluidic reactors can optimize mass and heat transfers like no other technique. As expected the protocol appears to be particularly suitable for heterogeneous liquid/liquid systems, where cavitation may disrupt the phase boundary that enhances
contact between reactants much more efficiently than under silent conditions. Experimental details may however be problematic as a micro-sonoreactor will also require a reduction in piezoelectric component size and this concern should be addressed in future studies. In fact, numerous applications simply immerse the meso- or micro-device in conventional cleaning baths to avoid fouling and clogging, common drawbacks under such operational conditions and compulsory if hazardous or toxic reagents are involved. A schematic illustration of the latter is supplied with Figure 8 dealing with the oxidative nitration of phloroglucinol (PG) leading to a hazardous trinitrate derivative (TNPG) under continuous-flow conditions [50]. The set-up consists of two separate feeds of PG and ammonium nitrate, which are pumped into a T-mixer and then a capillary tube (coil 1, 0.8 mm inner diameter) where efficient mixing occurs. As precipitation of the product is expected, coil 1 is further connected to a larger tube (coil 2, 1.6 mm inner diameter) and immersed in a thermostated US bath. A third capillary tube with a water stream has simply the purpose of quenching the transformation.

Figure 8. Schematic design for the nitration of phloroglucinol under continuous flow conditions. Reproduced with permission from ref. [50]. Copyright 2014 American Chemical Society.

A recent review has described previous efforts to merge microfluidics and sonochemistry for greener applications as well as the current state of the art [51]. Cavitational collapse in confined tubular media provides both chemical and physical effects which range from inducing the formation of excited intermediates through molecular fragmentation to merely promoting mixing or separation. It is fair to say that droplet technology in microfluidic chambers is well developed and so its scope will not be treated in detail here. These procedures however involve acoustic actuation at low frequencies which are not generally employed in sonochemistry and in which radiation pressure and acoustic streaming play pivotal roles [52]. Likewise, surface acoustic waves (SAWs), which operate at high frequencies (MHz region), and which are generated by applying an oscillating electrical signal to microelectrodes,
have been incorporated into microfluidic devices and enable droplet manipulation. SAWs have also been successfully applied to chemical synthesis and can often be superior to ultrasound itself in terms of energy density and approximately as efficient as MW [53]. Once again, the lesson to be learned is that clear-cut knowledge of the acoustic field is strongly required. Sonochemical activity depends on the type of flow, frequency and power setting which all affect radical production, sonoluminescence and fluid motion [54].

**Conclusion**

As depicted in the hierarchy diagram below, information and knowledge of specific techniques are derived from raw data through the understanding of relationships and then patterns. The relationship and synergy between US and other enabling technologies for chemical processes may help us to fully understand sonochemistry and its great potential. This presentation aims at unveiling the features and paths where sonochemistry meets other non-conventional techniques and highlight, whenever possible, comparative aspects and strategies to overcome hurdles. A multidisciplinary approach for improved understanding and the ability to predict future behaviour are key features of the scientific method. In other words, a holistic approach to process intensification and technological innovation is in our interests (Figure 9).

![Hierarchy Diagram](image)

**Figure 9.** The hierarchy diagram representing a holistic model of technological innovation including the main enabling technologies.

**References**


