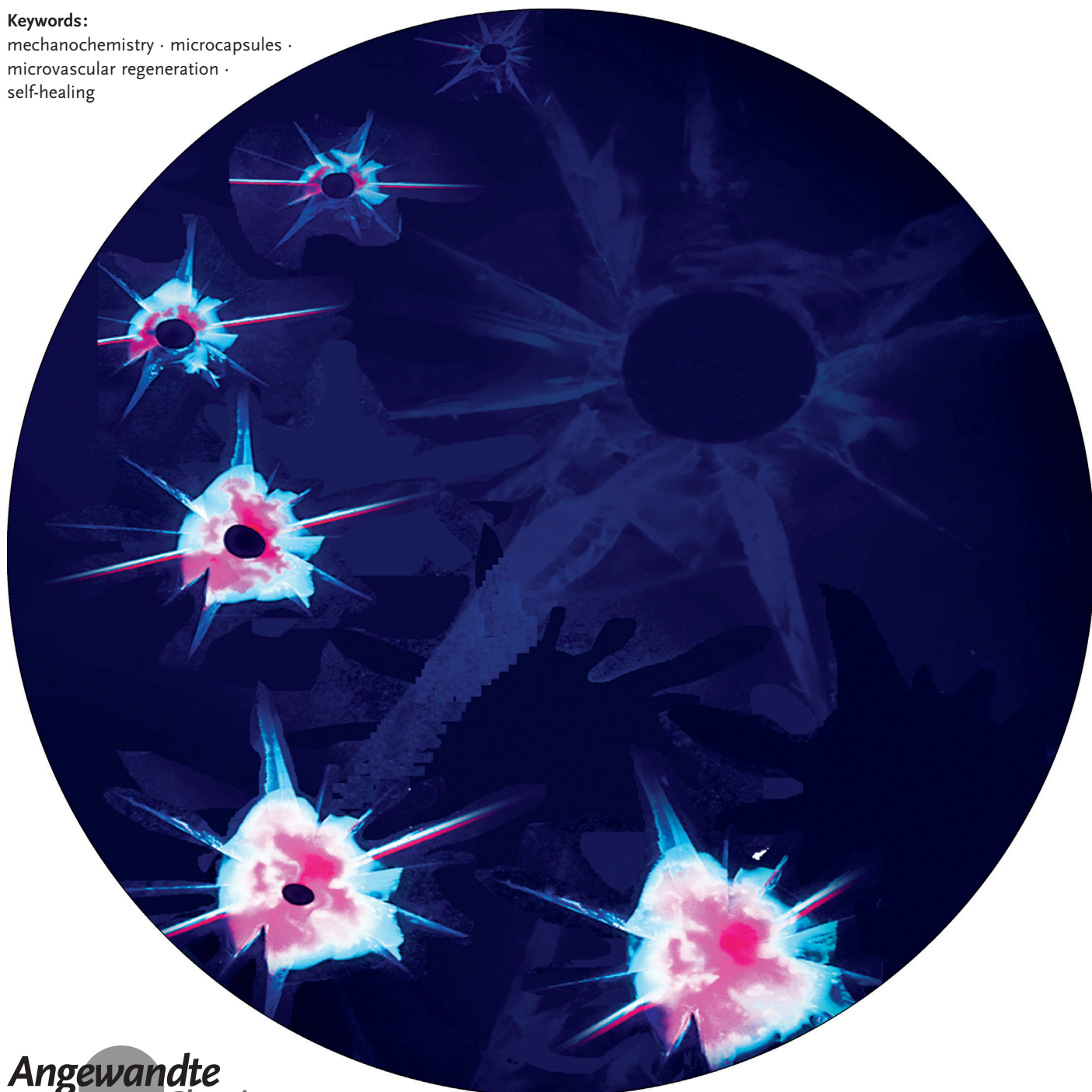


# Biomimetic Self-Healing

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**Keywords:**

mechanochemistry · microcapsules ·  
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self-healing



*Self-healing is a natural process common to all living organisms which provides increased longevity and the ability to adapt to changes in the environment. Inspired by this fitness-enhancing functionality, which was tuned by billions of years of evolution, scientists and engineers have been incorporating self-healing capabilities into synthetic materials. By mimicking mechanically triggered chemistry as well as the storage and delivery of liquid reagents, new materials have been developed with extended longevity that are capable of restoring mechanical integrity and additional functions after being damaged. This Review describes the fundamental steps in this new field of science, which combines chemistry, physics, materials science, and mechanical engineering.*

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## 1. Introduction

To heal is “to make whole or sound in bodily condition; to free from disease or ailment, restore to health or soundness; to cure (of a disease or wound).”<sup>[1]</sup> Self-healing provides an important evolutionary advantage,<sup>[2]</sup> since living organisms are affected both by intrinsic complications, such as side reactions and production of aggressive reactive intermediates,<sup>[3]</sup> and extrinsic menaces, mainly through the undesired transmission of energy to the living system. All organisms, from the smallest bacteria to the largest animals and trees, have different healing mechanisms—from proteins that fix DNA at the molecular level<sup>[4]</sup> to the regeneration of cells to seal a wound and restore the function of the damaged tissue.<sup>[2]</sup>

Self-healing is a thermodynamically expensive process, which leads towards organization (“negative entropy”).<sup>[5]</sup> Living organisms spend energy to adapt, maintain, or restore parts of their systems.<sup>[6]</sup> Synthetic materials are not capable of gathering energy and directing it towards self-procreation or healing, but, as in biomaterials, the adaptation and extension of the functional lifetime through healing is highly advantageous.<sup>[7]</sup> Thus, scientists have invested significant efforts in mimicking biological healing systems with synthetic materials. Inspired by biology, the necessary chemistry for the healing processes and delivery systems have been designed and created to provide nonliving synthetic materials with the ability to heal.

In this Review we describe the concepts, challenges, paradoxes, and different approaches to synthetic healing. We first describe examples of model biological systems, and then their different adaptations in synthetic materials. We first discuss intrinsic self-healing, where the chemistry of the material is designed to direct the mechanical energy from the damage to latent functionalities that lead to healing without the need for external materials. Next we consider extrinsic self-healing, where the healing chemicals are separated from the matrix and delivered upon damage. Finally, we examine biological regeneration and remodeling, which give certain organisms the ability to restore fully damaged organs.<sup>[8]</sup> Although regeneration has not yet been reproduced synthetically, we report on recent advances towards developing the necessary physics, engineering, and chemistry towards arti-

cial regeneration. We conclude the discussion with a perspective on the next challenges for the self-healing field.

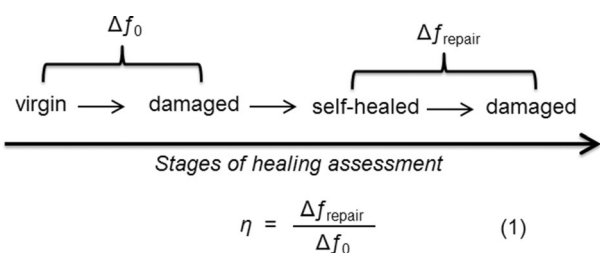
## 2. Concepts, Challenges, and Paradoxes of Self-Healing

Before focusing on biological and synthetic healing, it is important to understand the basic concepts, challenges, and paradoxes of self-healing.

The dictionary definition of “healing” provides a limited view of the concept—it works or it does not. To develop science and engineering, which can be measured, compared, and advanced upon, healing efficiency ( $\eta$ ) is defined by the percent recovery of a certain property or function [ $f$  in Equation (1)], which is evaluated by comparing virgin and healed materials (Figure 1).

It is important to clarify that healing a certain property of interest does not mean all properties of the material are restored. Healing physical damage to the spinal cord stops internal bleeding and restores most tissues and the circulatory

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**Figure 1.** Assessing the healing efficiency by comparing the change in the function of virgin and healed material.

system, but the nervous system is typically not recovered completely.<sup>[9]</sup> Physically, the damage is repaired, but not all functionality is restored. In synthetic materials, for example, a crack can be completely refilled with material, but the bulk strength or the fracture toughness might be lower than that of the original. Alternatively, fracture toughness might be fully restored, but the bulk strength of the material may be different. Importantly, partial recovery of function may be very significant in synthetic materials, especially when designing materials with specific uses or functions.

Autonomous self-healing is a concept constantly debated in the self-healing community. Biological self-healing is mostly autonomous; the living organism fixes itself using energy and material stored in the system, while continuing to absorb more energy and material from outside. Autonomous means self-controlled, automatic, without outside intervention, but what counts as outside intervention? Some prefer to connect autonomy to the source of energy; if the damaged material needs to be heated or irradiated, the self-healing is not autonomous, since an outside energy source was required.

But what if a sensory system detects damage and activates a circuit to heat the damaged area? What about pumps that circulate healing chemicals in a vascular system?<sup>[10]</sup>

Self-healing requires energy. Living systems constantly gather energy from the surroundings to sustain healing (and life itself), but they are still defined as autonomous. If the system uses electricity from an external (grid) or internal (battery) source, is that the difference between autonomic and non-autonomic? A different approach is to relate autonomy to human intervention. In this case, a fully automatized system with computers, pumps, and sensory systems that is connected to a battery or grid and is able to heat certain parts of the material and deliver healing chemicals is defined as autonomic, as long as all these processes are preprogrammed in the system. However, biological self-healing is “custom made” for specific materials and conditions, while synthetic systems aspire to be simpler and more general. Therefore, most studies do not consider the energy used for pumps as human intervention, but require the chemistry to work at room temperature.

An additional related topic is that of external intervention for crack closure. To assess healing efficiency and concepts, large cracks are often formed in test materials through mechanical failure. However, the crack surfaces are generally pressed together to register the crack faces and allow crack healing to progress. Although “human influence” is required to bring the two faces of the crack together, this act doesn’t generally preclude the distinction of “self-” or “autonomous” healing. Experimental necessity dictates that crack surfaces remain in proximity to assess healing efficiency while isolating the effects of crack geometry. Other than a single example at the end of this Review that deals with the healing of large



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volumes, all self-healing examples target micro- or nanoscale cracks in which the faces of the crack remain in proximity without the necessity of external intervention to press the faces of the crack together.

In biology, the healing of soft tissue (skin, for example)<sup>[11]</sup> is fundamentally different from the healing of hard tissue (bones, for example).<sup>[12]</sup> In soft materials, the constituents (polymer chains, proteins, cells) have a certain level of mobility, thereby allowing the healing chemicals to penetrate or react with the virgin material and create an indistinguishable interface.

In hard materials, the matrix molecules are static. The crack surfaces cannot come into full contact, thus making it a significant challenge for intrinsic self-healing. In extrinsic self-healing, even if a very reactive reagent is used, it will only react with the surface of the material, possibly producing a weak interface. A chemical healing process in which the adhesion strength is higher than the inherent material strength would provide a solution; however, this is difficult to accomplish in very hard materials, such as metals,<sup>[13]</sup> ceramics,<sup>[14]</sup> and composites,<sup>[15]</sup> and, therefore,  $\eta < 100\%$  is typically obtained. A biomimetic solution is to plasticize the surface of the crack so that the material temporarily behaves as though it was soft.<sup>[16]</sup>

An important paradox of self-healing related to the previous topic is the self-healing kinetics. Most healing processes in nature, when triggered, provide a fast response (self-sealing to stop bleeding, defend against infection, etc.),<sup>[17]</sup> followed by a slow process to restore homogeneity and function. In soft materials, such as the skin, a cut can be completely healed in a day, while in hard materials, such as a bone, the process takes over a month. In synthetic materials, a single fast step is expected to seal the damage and restore the material's properties. In many applications, self-healing needs to be fast or, for example, the airplane might lose air pressure, the bridge may fall, or the space rocket may explode as it is leaving the atmosphere. This is a fundamental point where synthetic healing diverges from biological healing.

Perhaps the biggest paradox of self-healing chemistry is the latency/reactivity of the chemical healing process. The components of the healing process need to be highly reactive to achieve fast and efficient reactions with solid surfaces. In intrinsic self-healing, highly reactive species are only produced in the material when damage occurs, whereas in extrinsic self-healing, the reactivity needs to stay active inside the material for as long as possible. The right balance between reactivity and stability provides the ideal chemical system for healing.

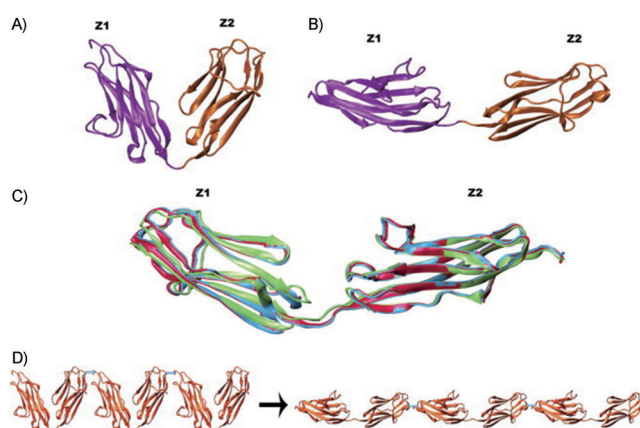
### 3. Intrinsic Self-Healing

Intrinsic self-healing is based on the chemistry of the material's matrix. In nature, evolution selected biomaterials by combining strong covalent bonds and weaker reversible bonds. However, designing a new material with intrinsic self-healing capabilities is challenging, and requires a profound understanding of how mechanical forces affect the material at the molecular level—plastic and viscoelastic deformation (the

interactions between molecules and positioning of the chains) as well as the covalent bonds which can undergo scission.<sup>[18]</sup> Although, hypothetically, any reversible reaction can be used to design an intrinsic self-healing system, the action of mechanical force on reversible bonds sometimes directs the reactions to different intermediates and products from the ones obtained by heating.<sup>[19]</sup>

#### 3.1. Biological Intrinsic Self-Healing

Examples of intrinsic self-healing in biology are numerous, and include repair at the molecular level up to polymeric tissues (such as the bone).<sup>[20]</sup> Titin is a protein that functions as a molecular spring in muscle.<sup>[21]</sup> Under mechanical stress (stretching), up to 244 individually folded domains unfold (Figure 2). When stress is released, the different domains refold.<sup>[22]</sup> At the molecular level, the folding of each domain is defined by collections of supramolecular interactions, which are broken under stress and reformed when relaxed.



**Figure 2.** A,B) Crystal structure of the N-terminal region of titin, which is comprised of tandem Z1 (purple) and Z2 (orange) domains in two crystallographically constrained conformations. C) NMR-RDC models of semiextended domains. D) Elasticity of the tertiary structure of titin. Reproduced from Ref. [22] with permission.

Many other relevant biomolecules use reversible supramolecular bonding for reversible mechanical behavior, and some also use disulfide bonds, although those demand more complicated redox chemistry.<sup>[23]</sup> Nature's strategy is to use sacrificial weak bonds to provide a self-repair mechanism in addition to the strong covalent bonds. Mechanical energy is relieved by scission of weaker bonds (hydrogen, disulfide), which reform thermally or chemically.

#### 3.2. Challenges in Synthetic Intrinsic Self-Healing

The design of functional groups that absorb mechanical energy to activate chemical bonds (mechanochemistry)<sup>[24]</sup> is challenging, since, in contrast to thermal or photochemistry, there is an additional directionality parameter (force vector) that alters the reaction plane according to the positioning of

each atom in relation to the force vector. The bond strength of the force-sensitive functional group (mechanophore) defines on one hand how selective the mechanochemical reaction is, and, on the other, how much energy it can dissipate. The reactive species formed needs to be stable enough to survive until it finds another reactant to form a new bond. If the kinetics of bond formation stipulates that additional energy needs to be added to the system for healing, then it is defined as a non-autonomic system. Most examples of synthetic intrinsically self-healing materials demand an additional input of energy (light or heat), while most biological materials use only the mechanical energy from the damaging event, thus providing a purely autonomic healing system.

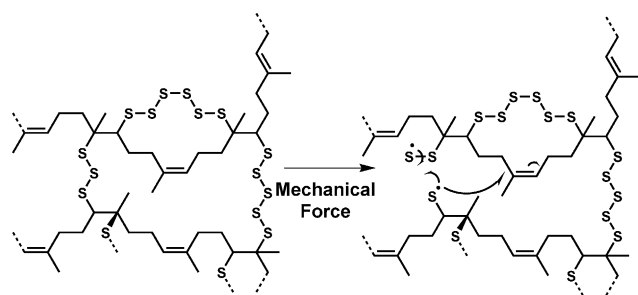
Since this type of healing occurs at the molecular level, the bond-forming reactions occur when the reagents are at nanometer distances at best, and large crack gaps are hard to heal. In soft materials, healing is achieved by manually bringing the two interfaces together; however, in hard materials the static surface typically does not allow for full contact and heating is required to impart the needed mobility.

### 3.3. Synthetic Intrinsic Self-Healing

The many different examples of synthetic intrinsic self-healing can be divided into three main strategies: Production of reactive species, production/activation of a catalyst, and disruption of a chemical equilibrium.<sup>[25]</sup>

#### 3.3.1. Production of Reactive Species

Mechanochemical degradation of materials characteristically produces reactive species through the transduction of mechanical energy into chemical energy. For example, when polystyrene is mechanically stressed, C–C bonds are cleaved homolytically, thereby producing two radicals that can be trapped and observed by ESR spectroscopy.<sup>[26]</sup> However, these reactive species typically degrade quickly and are not capable of forming new bonds. In the 1930s it was already found that vulcanized rubber could self-heal in the absence of oxygen.<sup>[27]</sup> The mechanical force in cross-links leads to scission of S–S bonds into long-lived sulfur radicals that, in the absence of oxygen, recombine or react with double bonds to form new S–S bonds or C–S bonds (Scheme 1).<sup>[28]</sup>



**Scheme 1.** Mechanochemical scission and self-healing in vulcanized rubber. Long-lived sulfur radicals can recombine or undergo addition reactions to double bonds, thereby forming new covalent bonds.

Other materials were found to intrinsically self-heal, such as soda-lime-silica glass.<sup>[29]</sup> Si–O bonds are broken homolytically and heterolytically to form reactive Si and O radicals that are capable of forming new bonds when heated in the absence of water and oxygen.<sup>[30]</sup> Polymers and ionomers were also found to be intrinsically self-healing if heated above the glass temperature ( $T_g$ ), when chains can re-entangle and noncovalent bonds reform.<sup>[31]</sup> Interestingly, Huang et al. demonstrated the use of transducing agents such as graphene embedded in the matrix to achieve healing when using different energy sources such as IR light, electricity, or electromagnetic waves.<sup>[32]</sup>

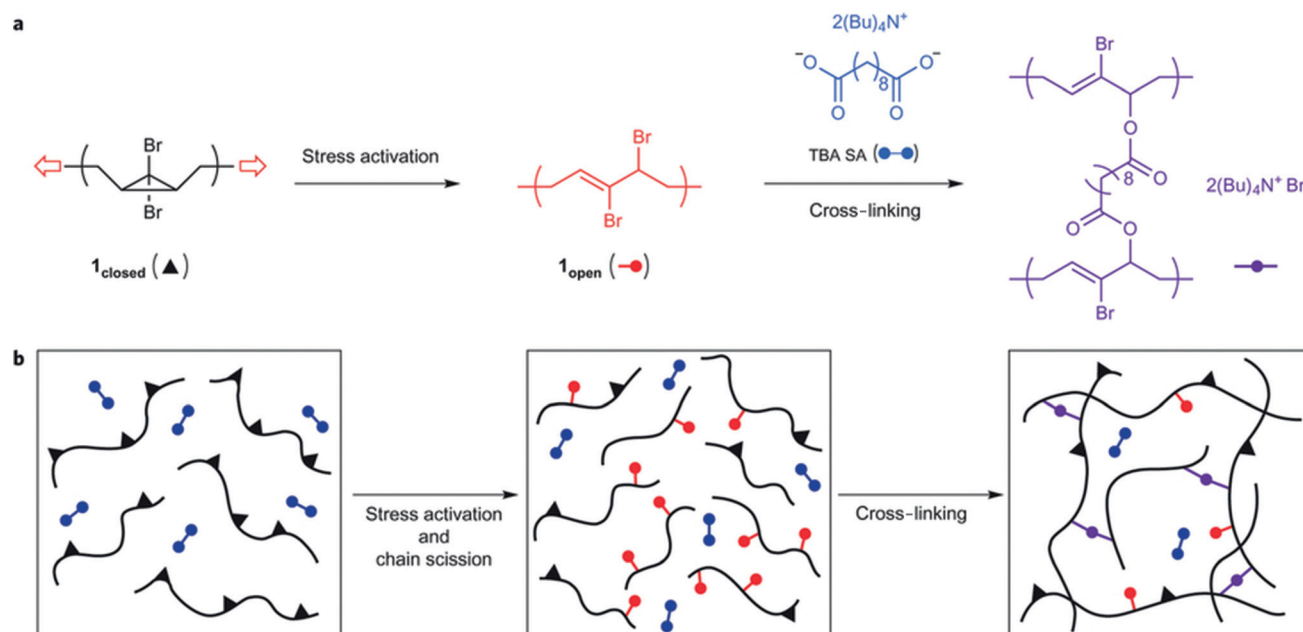
An initial design to produce stable, reactive radicals led to the development of azo mechanophores.<sup>[33]</sup> Upon scission, “stable” tertiary carbon radicals with an  $\alpha$ -nitrile group are produced. These radicals were produced in dilute polymer solutions through ultrasonication-induced solvodynamic shear, and they did not form new polymer–polymer bonds, but reacted with oxygen. Kryger et al. used a cyclobutane mechanophore to produce cyanoacrylates, which undergo polymerization in the presence of water.<sup>[34]</sup> Cyanoacrylate production was demonstrated using an excess amine trap, but self-healing was not demonstrated. A limitation of this approach is that, unless a cross-linked polymer is used, a single reactive site is produced per chain, thus reducing the chances of successful bond-forming events. Black-Ramirez et al. overcame this limitation by including numerous dihalocyclopropane mechanophores in the polymer.<sup>[35]</sup> Upon extrusion-induced tension of the bulk polymer, the dibromocyclopropanes underwent electrocyclic ring opening to 2,3-dibromoalkenes, which react with sebacic acid dianion present in the bulk (Scheme 2) to form new cross-links. In contrast to extrinsic self-healing, where a crack is needed to trigger the healing, self-healing occurs at the same time as the damage, and, in this case, a self-reinforcing effect is observed.

#### 3.3.2. Catalyst Production/Activation

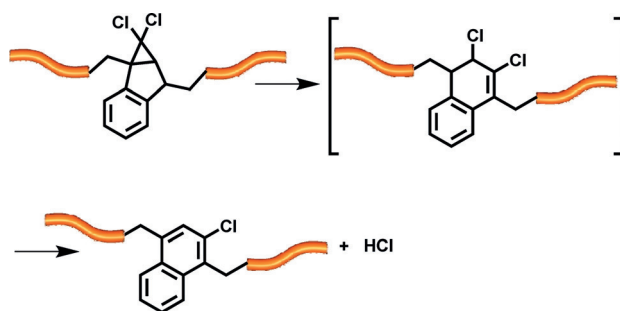
Since few mechanochemical events occur per chain in linear polymers, the production/activation of a catalyst, instead of a reactive species, can lead to the creation of many chemical bonds through turnover, for example, by cross-linking latent functional groups in side chains.

As a consequence of the interest in the mechanochemical activation of latent catalysts as an independent research topic, numerous catalysts have been studied. Examples include Ru benzylidenes for olefin metathesis,<sup>[36]</sup> Pd for cross-coupling reactions,<sup>[37]</sup> carbocations,<sup>[38]</sup> and silver for transesterification reactions.<sup>[39]</sup> Some of these catalysts were shown to induce polymerization in solution, but were not tested for self-healing. Bergman cyclization was induced through mechanochemical swelling<sup>[40]</sup> of cross-linked particles with monomer, thereby leading to its polymerization; however, there was no clear demonstration if the process was mechanochemical or thermal.<sup>[41]</sup>

A limitation of this strategy is the fact that the catalyst has a polymer tail, which limits its diffusion in the bulk, a requirement to achieve the desired turnover in the solid state. To overcome this limitation, Diesendruck et al. demonstrated



**Scheme 2.** a) Mechanochemical electrocyclic ring opening of dibromocyclopropane to give 2,3-dibromoalkenes, which react with sebacic acid to form new cross-links. b) Formation of cross-links in bulk polymer. Reproduced from Ref. [35] with permission.



**Scheme 3.** Production of HCl through mechanochemical electrocyclic ring opening followed by thermal elimination. Reproduced from Ref. [42] with permission.

the mechanochemical production of HCl in bulk poly(methylacrylate).<sup>[42]</sup> This strong acid can diffuse in the solid state and catalyze the ring-opening polymerization (ROP) of epoxides. However, the mechanophore was thermally unstable, and was not tested in self-healing processes (Scheme 3).

### 3.3.3. Disruption of a Chemical Equilibrium

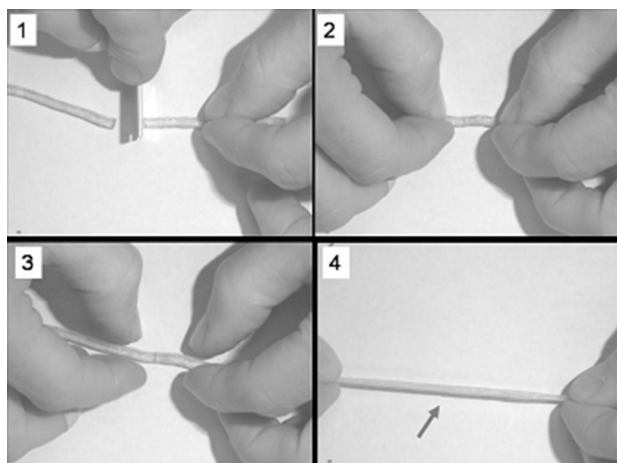
This intrinsic self-healing strategy is arguably the most successful one, and the closest to biological models. Chen et al. prepared a highly cross-linked material that had mechanical properties similar to epoxy resins through a Diels–Alder (DA) reaction.<sup>[43]</sup> Mechanical stress leads to retro-DA of the bicyclic cross-links. Re-equilibration is achieved with heating, which allows for chain mobility and creates more functional groups on the crack surfaces, thereby leading to full recovery of the material. Other materials with a large concentration of reversible strong chemical bonds were shown to be intrinsically self-healing; both thermosets<sup>[44]</sup>

and thermoplastics.<sup>[45]</sup> An interesting example was the demonstration that cross-linked polydimethylsiloxane (PDMS) prepared by anionic polymerization intrinsically self-healed upon re-equilibration of linear and cyclic oligomers.<sup>[46]</sup> A “catalyzed chain exchange reaction”, as proposed in 1954, was demonstrated as the self-healing mechanism in 2012.<sup>[47]</sup> Nonetheless, all these materials needed an additional input of energy, since the reversible bonds had high activation energy.

Bonds that equilibrate at room temperature allow for lower temperature healing. Grubbs catalyst embedded in cross-linked polybutadiene makes the C–C double bonds dynamic at room temperature, thus allowing for self-healing by pressing the two faces of the crack together.<sup>[48]</sup> Metal–ligand bonds were also shown to be reversible at room temperature, thereby leading to dynamic cross-links.<sup>[49]</sup> However, as in nature, hydrogen bonds provided the simplest and most effective autonomic self-healing for soft materials.

Cordier et al. prepared supramolecular rubbers based on hydrogen bonding between urea-functionalized polyamidoamines.<sup>[50]</sup> The equilibrated hydrogen bonds are cleaved upon cutting the rubber in two parts, which, if reconnected immediately, heals completely. However, if the parts are rejoined after a long delay, the healing efficiency is decreased due to re-equilibration in the separate parts.<sup>[51]</sup> Many different research groups explored other hydrogen-bonding units and produced a variety of soft materials with autonomous self-healing capabilities (Figure 3).<sup>[52]</sup>

The biggest challenge in hydrogen-bond-derived self-healing is to design a material that combines high modulus and toughness with an autonomic healing capability. Combining covalent and supramolecular cross-links improved the mechanical properties of the materials significantly.<sup>[53]</sup> A different approach based on phase-separated copolymers was



**Figure 3.** Autonomous self-healing rubber. Reproduced with permission from the CNRS image bank (phototheque@cnrs-bellevue.fr).<sup>[52]</sup>

demonstrated recently. In this case, the hydrogen-bond system is in the soft phase to provide self-healing capability and toughness, while a hard phase increases the modulus of the material.<sup>[54]</sup>

## 4. Extrinsic Self-Healing

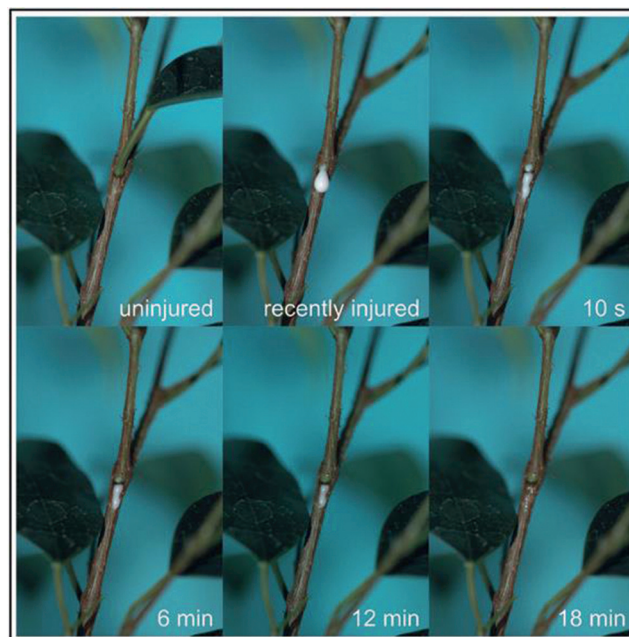
### 4.1. Encapsulation of Healing Substances

#### 4.1.1. Self-Healing Based on Biological Capsules

Of the different methods for self-healing, the use of capsules is the least common approach in nature, which encapsulates chemicals for numerous reasons other than self-healing. Cells can be seen as capsules with numerous internalized smaller capsules. Encapsulation separates the living from the nonliving (cell membrane), hydrolytic enzymes from the essential biomolecules (lysosomes), the genetic information from the rest of the cell (nucleus) etc.

Natural latex, an emulsion consisting of proteins, alkaloids, starches, oils, resins, and gums, is extracted from plants for our use as a rubbery material.<sup>[55]</sup> In some latex-producing trees, such as *Hevea brasiliensis*, the role of latex is to heal physical damage.<sup>[56]</sup> Latex is encapsulated in elongated cells called laticifers under high pressure (up to 15 bars). As a result of the difference in pressure, the emulsion is exuded when the tree is physically damaged, and encapsulated laticifers (capsules inside capsules) burst, thereby releasing hevein, a protein that induces latex coagulation (cross-linking), and closing the wound.<sup>[57]</sup> A similar mechanism is present in *Ficus benjamina* (weeping fig) and other plants of the genera *Euphorbia* and *Campanula*, with cross-linking times varying from a few seconds to around 20 min (Figure 4).

To summarize: A polymerizable solution is encapsulated under pressure, and bursts when physically damaged. An active catalyst for cross-linking the polymer that was not in contact with the monomer is also released upon physical damage. In the latex example, the catalyst was in smaller capsules inside the “monomer” capsule.



**Figure 4.** Observation of latex coagulation after injuring the bark of a weeping fig (*Ficus benjamina*).<sup>[58]</sup> After a few minutes, the latex is cross-linked, thereby sealing the wound. Reproduced with permission from C. A. Brebbia, A. Carpi: *Design and Nature* V, 2010, page 454.<sup>[58]</sup>

#### 4.1.2. Challenges in Self-Healing Based on Synthetic Capsules

The typically high reactivity of the healing chemicals means that not all encapsulation methods are practical, and efforts have been mainly focused on in situ and interfacial polymerization. Both techniques demand the production of a stable emulsion, using solvents that do not react with the healing substances. If water is used (and it typically is), the encapsulation of pure water-soluble reagents such as amines is a significant challenge.

Control over the size of the capsule is extremely important. Big capsules contain a larger volume of healing chemicals, thus allowing for healing of a larger crack. Furthermore, the “lost weight” (such as the membrane) is smaller. However, larger capsules will affect more significantly the properties of the material it is incorporated into, the propagation of cracks, and the roughness of the materials surface. Smaller capsules typically are limited in their healing ability because of the reduction in the volume of healing reagents that can be delivered, and, therefore, a higher ratio of capsule/material is required.<sup>[59]</sup> Micrometer-sized capsules have been used in most examples where synthetic self-healing has provided the best results, but techniques to make nanocapsules for self-healing have also been developed.<sup>[60]</sup>

Increasing the membrane thickness raises the stability of the capsules and reduces their permeability. However, it also increases the crack resistance of the membrane and reduces the ratio of encapsulated substances to membrane. The capsule membrane needs to bond well to the matrix so that cracks in the matrix lead to membrane failure. Capsules and their sensitive reagents must be present during fabrication, which may involve high-temperature curing. The capsule

contents must have long shelf-lives, yet be reactive with fast kinetics when needed.

The number of healing cycles for capsule-based systems is limited to one in each location. Once the healing substances are exposed and reacted, they can not be restored or replenished.

Healing processes require two components to meet only during a damage event: either two chemicals that react with each other or a monomer/initiator system. In the latex example described above, capsules inside capsules were used to separate the two components. However, this architecture is quite challenging to mimic and to date has not been reproduced for self-healing. Instead, other approaches have been used: the combination of capsules containing different fillers, dispersion of one of the reagents in the matrix, use of matrix functional groups (such as amine groups in epoxy resins), or gases from the environment (water or oxygen in air). The delivery and proper mixing of the two parts, especially in internal damage, can be problematic. In the biological example, the catalyst was already inside the monomer, and the pressured capsule helped with the mixing. Many of these challenges are common to extrinsic vascular self-healing since they use similar chemistry.

#### 4.1.3. Encapsulation Techniques for Self-Healing

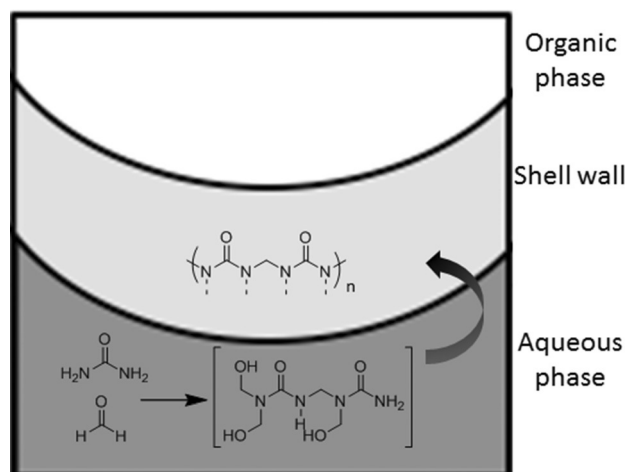
A recent review describes several methods for encapsulation.<sup>[61]</sup> The most common methods for self-healing applications are in situ and interfacial polymerization. In in situ polymerization, the monomers are soluble in one of the phases, and after a certain level of oligomerization, the polarity changes and the oligomers migrate to the second phase. Upon completion and cross-linking, the polymer forms a membrane around the second phase (the healing substances). This method has been used to prepare urea-formaldehyde (UF), melamine-formaldehyde (MF), melamine-urea-formaldehyde (MUF), and phenol-formaldehyde (PF) microcapsules (Figure 5).

In interfacial polymerization, two components coming from each of the phases react at the interface, thereby forming a polymer membrane around the smaller phase (Figure 6). This technique has been used to prepare polyurethane (PU) and polyacrylate (PA) microcapsules.

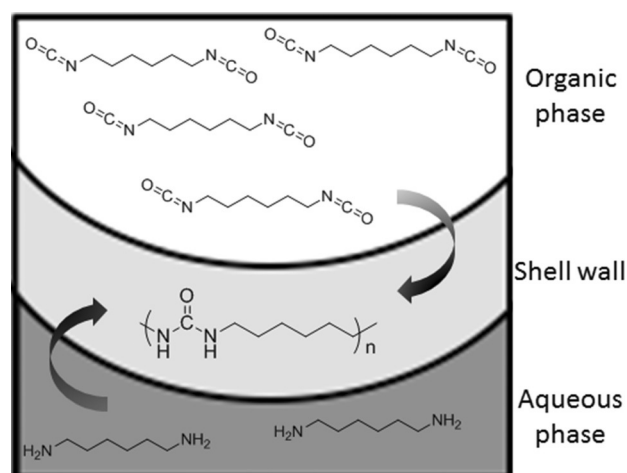
More recently, a new method for preparing microcapsules with double shell walls has been developed by combining in situ and interfacial polymerization.<sup>[62]</sup> These robust microcapsules contain an internal PU wall and an external UF wall (Figure 7). The chemistry of the internal PU shell is not yet clear, since it is not known with which component from the aqueous phase the isocyanate-rich PU prepolymer reacts.

#### 4.1.4. Synthetic Self-Healing through Encapsulation

Ring-opening metathesis polymerization (ROMP) of dicyclopentadiene (DCPD) was used in the first demonstration of synthetic autonomic self-healing (Scheme 4). DCPD-filled UF microcapsules<sup>[63]</sup> were dispersed in a diethylenetriamine (DETA) hardened epoxy (EPON 828; diglycidyl ether of bisphenol A (DGEBA)) matrix embedded with 1st gen-



**Figure 5.** Example of the in situ polymerization used for the synthesis of UF capsules. A prepolymer is prepared in the aqueous phase which migrates to the interface. Upon heating, the reaction is accelerated (elimination of water) and cross-linking occurs, thereby forming highly cross-linked UF polymer. Healing chemicals, solvents, surfactants, and emulsifiers are not shown.

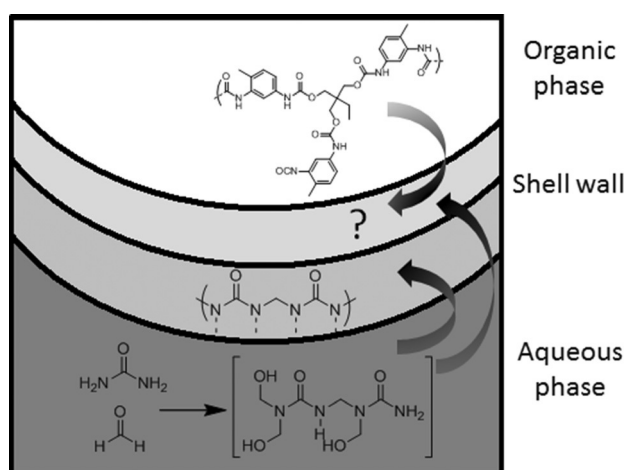


**Figure 6.** Synthesis of PU capsules exemplified with HDI and hexamethylenediamine. Healing chemicals, solvents, surfactants, and emulsifiers not shown.

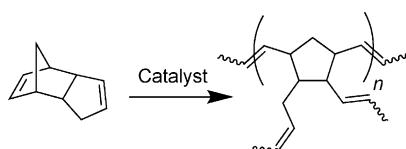
eration Grubbs catalyst.<sup>[64]</sup> Upon crack damage, the liquid healing agent was released and polymerized on contact with exposed catalyst, thereby rebonding the crack faces with cross-linked polydicyclopentadiene (pDCPD) and achieving an impressive 75% recovery of fracture toughness (Figure 8).

Several similarities are found between this system and the biological example (latex) described before: An encapsulated monomer is released and polymerizes/cross-links upon contact with the catalyst. However, there are a few significant differences. The catalyst is not encapsulated inside the monomer capsule, but is dispersed in the matrix. Furthermore, the capsules are not pressurized. These differences led to limitations in healing efficiency as a result of problems in mixing the monomer and catalyst, as well as reduced catalyst stability.<sup>[65]</sup>

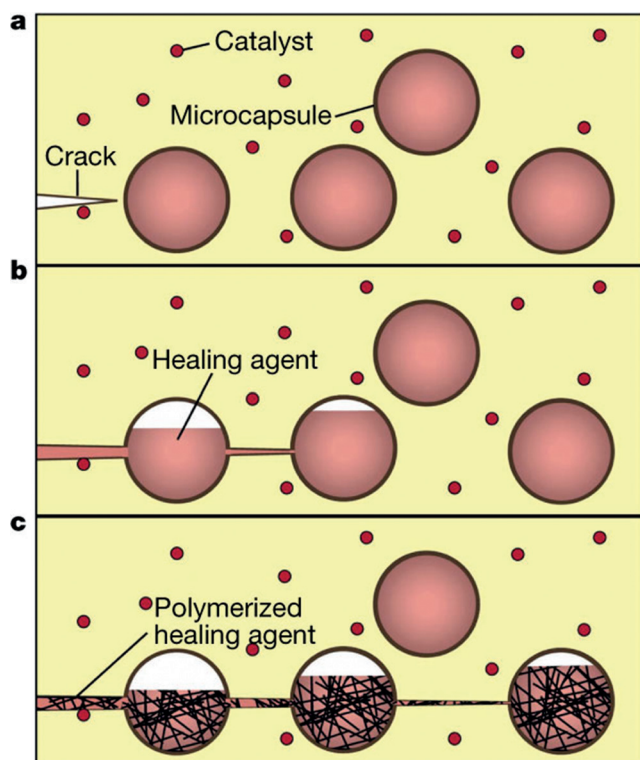




**Figure 7.** Synthesis of PU/UF microcapsules with double shell walls. In situ polymerized UF migrates to the interface, where isocyanate-rich PU prepolymer is cross-linked. Healing chemicals, solvents, surfactants, and emulsifiers not shown.



**Scheme 4.** ROMP of DCPC to form the highly cross-linked pDCPD.

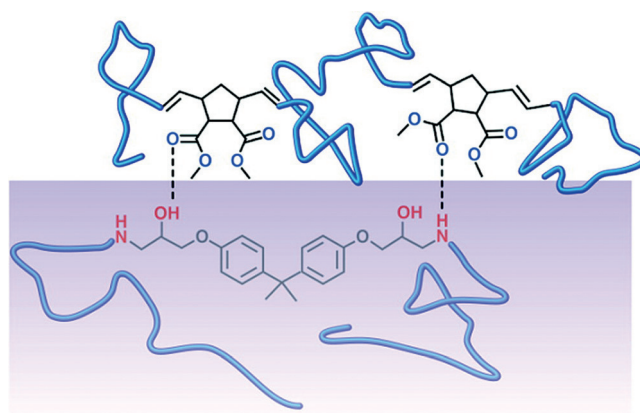


**Figure 8.** Self-healing with microencapsulated DCPD (pink) and dispersed Grubbs catalyst (red). Upon crack formation, DCPD flows in the crack plane and forms pDCPD (black) on contact with the catalyst. Reproduced from Ref. [64] with permission.

Encapsulating the catalyst in wax improved the healing efficiencies to almost 100% despite using a lower catalyst loading, but the thermal stability of the catalyst remained an issue.<sup>[66]</sup> The system was optimized by testing different catalysts, but faster initiating catalysts did not provide improvement since the characteristic faster polymerization in solution was not reproduced in the solid state.<sup>[67]</sup> A cheaper and more stable catalyst,  $WCl_6$ , was also tested, and demonstrated a longer lifetime. However, dispersion of this catalyst in the matrix was problematic and significantly affected the healing efficiency.<sup>[68]</sup> Other parameters optimized were the size and concentration of the DCPD microcapsules,<sup>[59]</sup> which affected not only the amount of healing agent delivered (and healing), but also the peak energy before failure; the morphology of the catalyst particles;<sup>[69]</sup> and the use of additives such as shape-memory alloys, which reduced the crack separation.<sup>[70]</sup> However, achieving close to 100% healing in an amine-hardened epoxy material certainly validated capsule-based healing as an approach to self-healing.

The main limitation of this healing chemistry is the poor bonding between the formed pDCPD and the virgin material, as no bonds are made between the materials. Wilson et al. introduced a co-monomer, dimethylnorbornene ester (DNE), to improve the adhesion of the healing film through hydrogen bonds with the matrix (Figure 9).<sup>[71]</sup> The optimized mixture of DCPD and DNE led to an increase in the peak load and shear strength after healing.

DCPD microcapsules were also tested in the self-healing of other materials. Fiber-reinforced epoxy composites are more challenging to heal,<sup>[72]</sup> since the healing agent has to adhere to both the matrix and unbonded fibers, which present completely different surface chemistry.<sup>[73]</sup> Self-sealing was successful using DCPD microcapsules,<sup>[74]</sup> but self-healing of interlaminar fracture toughness was limited on average to 38% at room temperature.<sup>[75]</sup> Heating the sample to 80 °C led to an average healing efficiency of 66%. In controls, where the healing agent was manually injected, 100% recovery was observed, thereby indicating that optimization of the delivery of the healing agent or mixing with the catalyst was still possible. The addition of core-shell nanofibers filled with



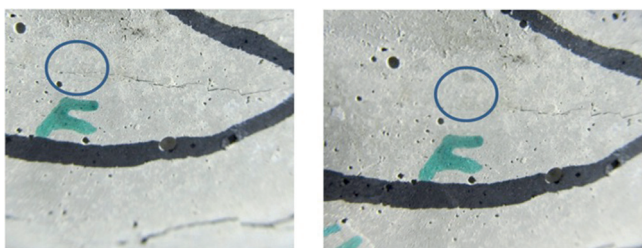
**Figure 9.** Hydrogen bonding between epoxy resin and poly(DCPD-co-DNE). Reproduced from Ref. [71] with permission.

DCPD to carbon-fiber epoxy composites allowed for better delivery of the healing agent, and good healing of flexural stiffness was achieved using a volume fraction of the nano-fiber of less than 1%.<sup>[76]</sup>

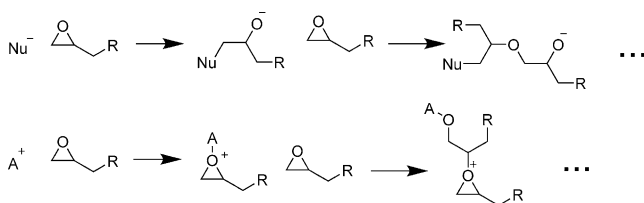
A high healing efficiency of over 80% was also obtained in commercially significant epoxy vinyl esters<sup>[77]</sup> and in bone cement, which is composed mainly of thermoplastic PMMA and barium sulfate. Improving the resistance of bone cement to fatigue-crack propagation may contribute to an increase in the *in vivo* longevity of cemented total-joint replacements.<sup>[78]</sup> Using DCPD, the crack propagation rate in bone cement was between 2 and almost 10 times slower, depending on the DCPD/catalyst ratio.

Recently, DCPD microcapsules were tested in the development of self-healing concrete,<sup>[79]</sup> the idea being that the formed cross-linked pDCPD will be able to bond to concrete particles. Interestingly, the healing efficiency depended strongly on the pH value used during the preparation of the microcapsules, which defined the size of the microcapsules. The use of only 0.25% healing agent resulted in the pDCPD filling an induced crack (Figure 10) and restoring the modulus of elasticity to above that of the virgin material.

A similar monomer/catalyst healing chemistry is the ring-opening polymerization (ROP) of epoxides (Scheme 5). This chemistry is compatible with many epoxy resins, and may lead to covalent binding between the matrix and the healing film.



**Figure 10.** Crack filling with pDCPD from microcapsules. Reproduced from Ref. [79] with permission.



**Scheme 5.** Nucleophile (Nu) and acid (A) initiated ROP of an epoxide; only the most probable product is shown.

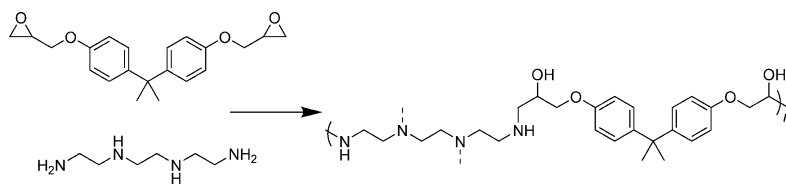
Rong et al. dispersed  $\text{CuBr}_2(2\text{-methylimidazole})_4$  in an amine-cured epoxy matrix. The imidazole remains mostly unreacted during curing, since the primary amine hardener is consumed much faster.<sup>[80]</sup> UF microcapsules filled with DGEBA are used as the second part of the healing system.<sup>[81]</sup> Healing at approximately 140 °C results in ROP of DGEBA being

triggered by the imidazole, thereby providing a 111% restoration of the fracture toughness. Healing efficiencies of fracture toughness up to 51% efficiency were obtained in the more challenging woven glass fabric/epoxy composites.<sup>[82]</sup> Impact damage in this material was healed more successfully, achieving close to 100% healing efficiency with a 1.5 J impact, and up to 90% with a 2.5 J impact.<sup>[83]</sup> Recently, Hart et al. tested 2-ethyl-4-methylimidazole as an initiator to reduce the healing temperatures, and obtained complete healing of the matrix at 100 °C.<sup>[84]</sup> Furthermore, they were able to demonstrate that not all imidazole is consumed in the first healing cycle, and carried out eleven healing cycles (with decreasing healing in each cycle) by adding more DGEBA manually.

Acids were also used as catalysts; however, they needed to be encapsulated so they didn't react with the hardener. Xiao et al. combined vacuum-infiltrated PA microcapsules with  $\text{BF}_3\cdot\text{OEt}_2$ <sup>[85]</sup> and DGEBA, which provided recovery of over 80% of the impact strength within 30 min at 20 °C.<sup>[86]</sup>

Curing epoxy resins with a hardener leads to the formation of a stronger material that is also compatible with epoxy matrices (Scheme 6). However, encapsulating amines (hardener) is challenging, since they are soluble in both water and organic solvents. Instead, hydrophobic complex thiols in MF microcapsules in combination with diglycidyl tetrahydro-*ortho*-phthalate were used by Yuan et al. to heal an amine-hardened epoxy matrix and achieve over 100% healing efficiency of the fracture toughness after 24 h at room temperature.<sup>[87]</sup>

Given the success of resin/hardener healing chemistry in vascular healing (see Section 4.2.3), additional efforts were taken to encapsulate aliphatic amines to develop a similar two-capsule system. Microfluidics were used to prepare PA microcapsules filled with aqueous DETA; however, these microcapsules have much thicker shell walls than UF microcapsules prepared by *in situ* polymerization.<sup>[88]</sup> McIlroy et al. prepared PU microcapsules in an organic-organic emulsion, where the polar amine (excess DETA reacted with DGEBA) separates from the cyclohexane solvent.<sup>[89]</sup> However, the microcapsules were too brittle and tended to break upon mixture with the matrix. The authors added a second wall of polyamide, but the shell wall became quite thick and the internal volume was significantly reduced. This approach was further optimized by using interfacial polymerization in a nanoclay suspension in decalin to make PU microcapsules.<sup>[90]</sup> However, the shell walls were still thicker than in typical PU microcapsules. Recently, Li et al. used reversed Pickering emulsions to encapsulate aqueous tetraethylenepentamine (TEPA), an aliphatic liquid hard-

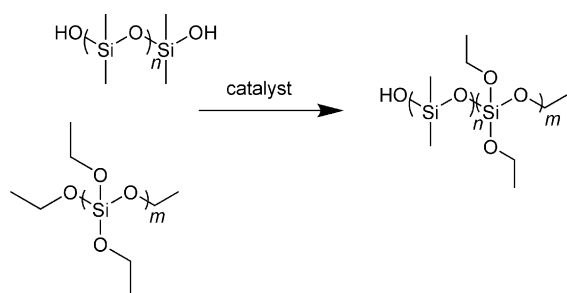


**Scheme 6.** Curing epoxy resin (DGEBA) with a hardener (DETA); only one of several possible products is shown.

ener, in PU microcapsules.<sup>[91]</sup> Capsules with typical shell-wall thicknesses were obtained, and the filling was 33% amine.

In another approach, hollow UF microcapsules were infiltrated with amines under vacuum, and in combination with resin microcapsules provided 91% healing efficiency in a low-temperature-cured epoxy matrix.<sup>[92]</sup> However, the amine microcapsules were shown to leak during curing at high temperatures. Polyoxypropylenetriamine-infiltrated PU/UF microcapsules provided fracture toughness healing efficiencies of over 90% in matrices that underwent a postcure process at 121 °C, and about 85% if postcuring was carried out at 150 °C.

Polydialkylsiloxanes are low-cost, water-, air-, and heat-stable elastomers with low  $T_g$  values that can flow into cracks and undergo a cross-linking reaction. The polycondensation of phase-separated hydroxy end functionalized polydimethylsiloxane (HOPDMS) and polydiethoxysiloxane (PDES) was carried out with PU-encapsulated tin catalysts (Scheme 7) to heal vinyl ester<sup>[93]</sup> and high-temperature

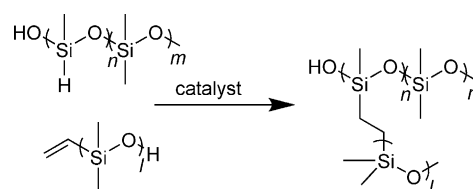


**Scheme 7.** Simplified reaction between HOPDMS and PDES. Additional bonds are formed between different hydroxy terminals and ethoxysiloxanes to form a cross-linked material.

amine-cured epoxies.<sup>[94]</sup> However, since the healing system forms a soft polymer, healing of the critical fracture load reached only approximately 24%. Healing of an epoxy vinyl coating, where healing efficiency was defined as corrosion inhibition, was much more successful, and improved significantly the protective properties of the epoxy vinyl coating after mechanical damage.<sup>[95]</sup>

This healing system becomes much more significant when used in softer materials, such as PDMS. Self-sealing of punctured flexible PDMS laminates was achieved, with the healing efficiency depending highly on the puncture size and microcapsule size—that is, the results depended on the volume ratio of healing chemical to lost volume.<sup>[96]</sup> Complete self-sealing was achieved for punctures up to 0.49 mm diameter.

Platinum-catalyzed hydrosilylation has also been used for cross-linking (Scheme 8). Two UF microcapsules filled with PDMS copolymer with active silane sites and high-molecular weight vinyl-functionalized PDMS and a platinum catalyst were used to heal PDMS after a tear test; recovery of at least 70% of the original tear strength (with some cases even surpassing 100%) was obtained.<sup>[97]</sup> In the healing of torsion fatigue, a 24% reduction in the total crack growth was achieved.<sup>[98]</sup>



**Scheme 8.** Simplified reaction between vinyl-terminated PDMS and hydrosilyl-containing PDMS. Additional bonds are formed between different hydroxy terminal groups and ethoxysiloxanes, which lead to a cross-linked material.

All these examples indicate that encapsulation allows for any polymerization chemistry to be used for self-healing. Some additional self-healing systems tested include reactive diisocyanates<sup>[99]</sup> (used in the healing of epoxy coatings for corrosion inhibition),<sup>[100]</sup> autonomic “click” chemistry (used to heal a high-molecular-weight polyisobutylene matrix),<sup>[101]</sup> Diels–Alder adducts (to heal amine-cured epoxy thermosets that had a diene covalently linked to the matrix),<sup>[102]</sup> and radical polymerization (tested in the self-healing of epoxy vinyl ester resins).<sup>[103]</sup>

A simpler encapsulated healing system uses solvents to dissolve/swell/plasticize the polymer chains, thereby allowing them to re-entangle.<sup>[104]</sup> With time, the solvent evaporates and/or diffuses away into the material to low concentrations. Caruso et al. manually tested several organic solvents by inducing a crack in an amine-cured epoxy and manually adding a small amount of solvent to the crack plane.<sup>[105]</sup> The two faces were realigned, and allowed to heal for 24 h at room temperature. Nitrobenzene, *N*-methyl-2-pyrrolidone (NMP), dimethylacetamide (DMA), dimethylformamide (DMF), and dimethylsulfoxide (DMSO) displayed the best results; unfortunately, their encapsulation was unsuccessful at the time. Therefore, UF-encapsulated chlorobenzene (20 wt%) was tested, which provided 82% fracture toughness healing.<sup>[106]</sup> Importantly, this value is comparable to the healing obtained by manual addition of the solvent (76%), thus indicating good delivery (wetting/diffusion) of the solvent in the plane of the crack. A limitation of this system is that the two faces of the crack need to be in close contact, thus making this healing system suitable for microcracks, but not larger modes of damage. As in the case of DCPD healing, the use of shape-memory alloys can improve healing by reducing the crack separation.<sup>[107]</sup> Another limitation is the need to have the matrix undercured such that there are sufficient quantities of reactive functional groups to bring about changes to the matrix covalent bonds.

DGEBA was coencapsulated with ethyl phenylacetate (EPA), a nontoxic alternative to chlorobenzene.<sup>[108]</sup> The matrix contains unreacted amine groups that are exposed during swelling and react with DGEBA to form new chains in addition to the induced formation of entanglements, which raises the healing efficiency to over 100% under identical conditions and lower microcapsule content (15 wt%).<sup>[109]</sup> Importantly, the amount of resin in the capsules had to be tuned, since the healing efficiency was significantly lower at high concentrations.

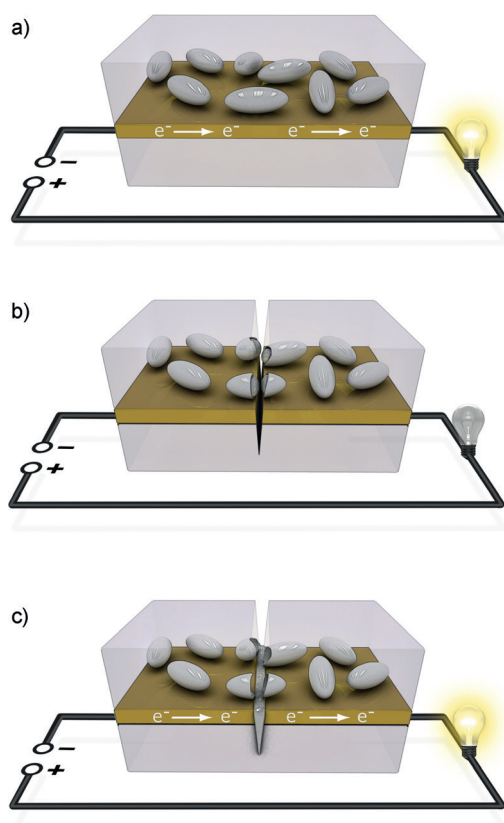
Solvent/resin microcapsules were functionalized directly on the surface of fibers to test the self-healing of interfacial

strength between the fibers and matrix.<sup>[110]</sup> An impressive 86% (average) healing was achieved after 24 h at room temperature for glass fibers,<sup>[111]</sup> and up to 91% in the case of carbon fibers.<sup>[112]</sup> These two examples demonstrate the power of this simple self-healing system.

#### 4.1.5. Restoration of Conductivity

Self-healing a function such as electrical conductivity requires a healing system that is (or becomes) a conductive material, and creates physical and electrical integrity between crack faces. Self-healing of conductivity has become an important field of research especially in the area of lithium batteries, where charging and discharging lead to mechanical degradation of the anode.<sup>[113]</sup>

The first studies on the self-healing of conductivity used UF microcapsules filled with carbon nanotubes (CNTs) dispersed in chlorobenzene or EPA to potentially provide both mechanical (solvent) and conductivity (CNT) healing.<sup>[114]</sup> These microcapsules were tested by embedding them in layers of epoxy above and below a glass slide patterned with gold lines.<sup>[115]</sup> Sample fracture resulted in the conductivity being lost as a crack formed in the gold line. The release of carbon nanotube (or graphene) suspensions restored the conductivity after a few minutes (Figure 11). However,



**Figure 11.** Testing self-healing of conductivity in a gold line: a) before damage; b) immediately after damage, the fracture of the gold line destroys the conductivity; and c) after healing of the conductivity in the gold line. Reproduced from Ref. [115] with permission.

restoration of the mechanical integrity of the epoxy layer was not described.

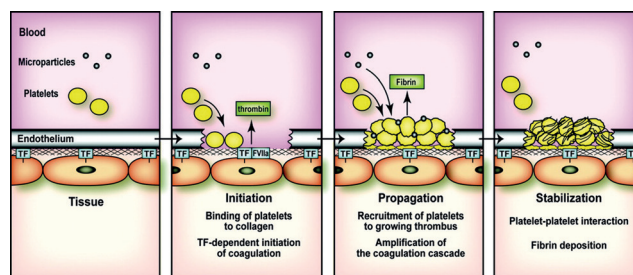
Other conductive chemical systems were similarly encapsulated and tested, including tetrathiafulvalene (TTF) and tetracyanoquinodimethane (TCNQ) which form conductive TTF-TCNQ crystals,<sup>[116]</sup> a liquid metal mixture of gallium and indium,<sup>[117]</sup> and more recently, carbon-black (CB) dispersions,<sup>[118]</sup> which is especially attractive, since CB is already used as a conductive additive in graphite anodes. In combination with co-encapsulated poly(3-hexylthiophene) (P3HT), a silicon anode cracked with a 10  $\mu\text{m}$  linear crack had its conductivity restored with efficiencies in the range of 95 to 100%. This promising self-healing system certainly increases the chances of a practical silicon anode for a lithium-ion battery, which rapidly loses integrity because of its approximate 400% volume change during lithiation.<sup>[119]</sup>

## 4.2. Vascular Healing

### 4.2.1. Biological Vascular Healing

Vascular systems are a prerequisite for multicellular organisms, since mass transport between the different parts of the body is necessary for the organism to work. Our circulatory system, pumped by the heart, is responsible for delivering nutrients, oxygen, heat, hormones, defence cells, as well as “healing chemicals” to damaged tissues. Circulatory systems are present in all vertebrates and also in most invertebrate animals. When a circulatory system is absent (some animals and plants), noncirculatory hyperbranched vascular systems direct the diffusion of nutrients to all cells.

When a tissue is physically damaged, the damage might reach the circulatory system, which releases its contents into the crack space (bleeding). Since the circulatory system transports nutrients and energy, a fast self-sealing occurs to stop bleeding. In humans, the self-sealing occurs through a fast coagulation, called haemostasis. During haemostasis, platelets from the blood “cross-link” through binding between fibrinogens and glycoproteins, and bind to the exposed collagen from the skin through specific glycoproteins (Figure 12).<sup>[120]</sup> The circulating red blood cells are caught in the platelet network and lead to coagulation, during which prothrombin is proteolytically cleaved to form thrombin, a serine protease that converts soluble fibrinogen into insoluble strands of fibrin. The fibrin binds all the different cells together, thereby reinforcing the platelet plug.



**Figure 12.** Formation of a clot at the site of blood vessel injury. Reproduced from Ref. [120b] with permission.

The repair process is not finished with the self-sealing.<sup>[121]</sup> After cleaning the wound from bacteria and debris (phagocytosed by white cells), growth factors are released from the platelets inducing cellular proliferation. New blood vessels are formed<sup>[122]</sup> and collagen and fibronectin are deposited to provide a temporary extracellular matrix, which directs newly produced epithelial cells to move into the wound.<sup>[123]</sup> Finally, a remodeling process occurs, whereby collagen is realigned along tension lines, and cells that are no longer needed are removed by apoptosis.

To summarize: damage cracks expose the pressurized liquid inside the vascular system which rapidly reacts with itself and the matrix to seal the wound. In a second step, new matrix and vascular vessels are created and the temporary sealing removed.

#### 4.2.2. Challenges in Synthetic Vascular Healing

Many of the challenges of vascular self-healing are common to encapsulation-based self-healing. The reactive healing chemicals are not encapsulated, but come in contact with the different parts of the system: channel walls, matrix, pumps, seals etc. If the vascular system is directly carved in the matrix, the liquid healing chemicals should not swell or react with it. Alternatively, the preparation of microvascular vessels requires more complicated engineering of the system, but allows the use of reagents that react with the matrix chemistry. In this case, an important advantage is the fact that the sensitive healing chemicals need not be present during fabrication but are added when the device is in use. Furthermore, the healing chemicals can be changed when the end of their shelf-life is approaching.

As in the case of microcapsules, the healing systems require two components to remain inactive until polymerization is triggered by the mechanical damage. In microcapsule self-healing, many examples used two-capsule systems. In vascular systems, two independent circulatory systems are required, further complicating the engineering. In this case, it is important that no diffusion of chemicals occurs between the two vascular systems. Two-part healing systems also require a certain stoichiometry and good mixing, which is problematic when viscous liquids are used.

The size of the microchannels and the pumping rate are important factors in defining the amount of healing chemicals delivered, as well as the energy spent to keep the circulatory system at work. The distance of the vascular system from the surface affects the amount of damage necessary to trigger the healing system.

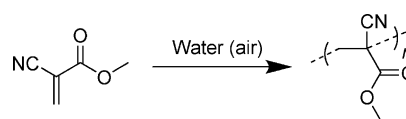
Another challenge is to achieve the full potential of vascular self-healing and achieve a high number of healing cycles. The vascular system is restored concurrently with the new matrix in biological self-healing; however, in synthetic self-healing, the healed area gets isolated from the vascular system and deeper damage is necessary to reach it again.

#### 4.2.3. Synthetic Vascular Self-Healing

Although microcapsules can be added to matrices as an additive, the cost of designing, preparing, and maintaining

a vascular system is higher. Therefore, vascular systems for self-healing are typically engineered for more complex and expensive materials, such as aerospace composites and batteries.

Several different “tubes”, such as hollow aluminum and copper cylinders, have been tested for delivering healing chemicals to a crack created by mechanical damage.<sup>[124]</sup> However, these metallic tubes are stronger than a polymer or a concrete matrix and failed to deliver the healing chemicals. Glass, on the other hand, survives thermal processing to make a composite and breaks easily upon mechanical damage. The use of pipettes as hollow glass fibers (HGFs) to create a model 1D vascular system started as early as 1993.<sup>[125]</sup> Dry and Sottos applied an epoxy polymer coating on glass pipettes filled with adhesives, and observed their release upon fiber-pulling experiments. A qualitative measurement of fiber rebonding during bending tests was carried out, using a one-part cyanoacrylate adhesive (Scheme 9) or



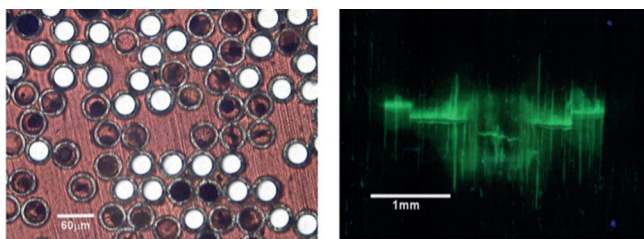
**Scheme 9.** One-component adhesive polymerization of cyanoacrylate. Weak nucleophiles start the polymerization, such as water from the air, thus making this an “air-curing” adhesive.

two-part epoxy adhesive (Scheme 6), with both giving positive results.<sup>[126]</sup> Dry also used this method to induce self-healing in concrete using acrylate polymerization, but the chemistry chosen did not have a long shelf-life, and the pipettes tended to randomly crack in the concrete.<sup>[127]</sup> HGFs coated with a brittle sealer were, therefore, used during testing to protect the vascular system.

This proof-of-concept had several problems that needed to be addressed, but just like in microcapsule self-healing, the remarkable success in the first published study demonstrated the potential of the method. Some of the questions to be addressed were the healing chemistry (cyanoacrylates do not have a long shelf-life and are not thermally stable for high-temperature curing) and the diameter of the tubes was too high, which affected the properties of the materials.

Bleay et al. introduced the idea of using micrometer-sized HGFs to both reinforce the composite and deliver the healing chemicals.<sup>[128]</sup> Vacuum-infiltrated 15  $\mu\text{m}$  diameter HGFs with a two-part epoxy adhesive were incorporated in an epoxy matrix. The samples underwent impact testing, and it was shown that the HGFs ruptured. Upon heating, the viscosity of the parts decreased and they flowed into the cracks. However, healing was minimal due to the difficulties of delivering the healing chemicals and curing. Pang and Bond improved the system by using larger borosilicate HGFs (60  $\mu\text{m}$ ).<sup>[129]</sup> In this case, delivery of the chemicals (Figure 13) and self-healing was clearly observed; nevertheless, the system lost its self-healing capabilities with time, through degradation of the resin.

The development and optimization of this two-part epoxy healing continued on 1D HGFs in different composites;



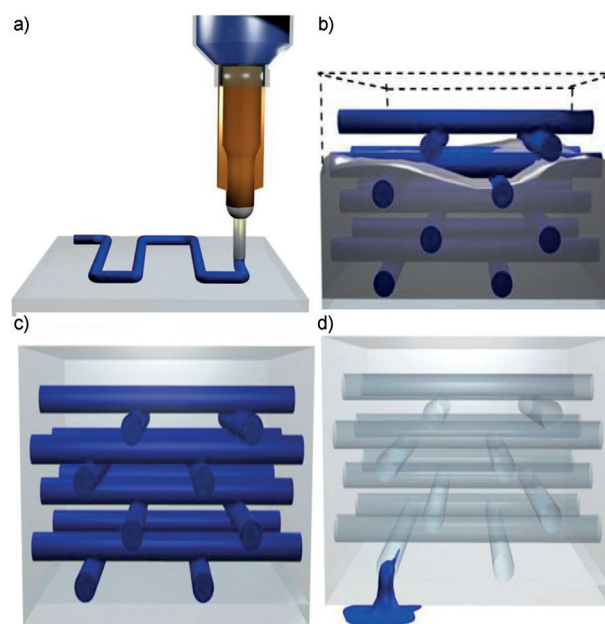
**Figure 13.** Left: 60  $\mu\text{m}$  HGFs embedded in a composite reinforced with glass fibers. Right: Bleeding of fluorescent dye from ruptured HGF in a damaged composite laminate. Reproduced from Ref. [129] with permission.

however, this method still had significant limitations, such as the large amount of damage required to rupture the vessels and reliance on capillary forces to distribute the healing agents.<sup>[130]</sup>

A partial solution to these problems came through expanding the dimensionality of the vascular system. Bond and co-workers developed a 2D interconnected vascular network in a structural composite sandwich panel. Larger (1.5 mm) vertical channels were directly carved into the matrix, penetrating 1.5 mm PVC hollow tubes, and the healing chemicals were delivered under positive pressure.<sup>[131]</sup> In half of the tested samples, both resin and hardener infiltrated the crack and restored the original failure mode and failure load; in the other half, only one of the parts was delivered, which provided no healing. Delamination healing was also studied through a drop weight test, which resulted in channel rupture and release of the healing agent.<sup>[132]</sup> In this case, significantly different results were obtained depending on the pressure of the vascular system. Under low pressure (5.6 kPa), only a moderate recovery was measured after 48 h at room temperature and an additional hour at 60 °C. When a higher delivery pressure was used (0.2 MPa for 48 h), under otherwise identical healing conditions, full in situ recovery of the debonded core–skin interface was obtained. These studies again point to the challenges in delivery and mixing in two-part healing systems.

A different approach to create vascular systems inside a matrix is to add a mould made of another material before matrix polymerization and then remove it after the matrix is solid. This approach was used to create a 3D vascular system using a “fugitive organic ink” scaffold that was deposited using a 3D printer (Figure 14).<sup>[133]</sup> The “fugitive organic ink” is a mixture of high- and low-molecular-weight hydrocarbons that partially crystallizes upon deposition and becomes solid upon cooling.<sup>[135]</sup> The 3D structure of the mould is programmed in the computer, and “printed” by a robotic arm using a micronozzle of the desired channel size. The mould is frozen in dry ice/acetone to  $-70\text{ }^{\circ}\text{C}$  before the resin is infiltrated. After curing, the ink is removed by heating to reduce the crystallinity of the ink, which is removed under a light vacuum. A limitation of this strategy is that only low-temperature-cured epoxies can be used.

This system was first tested in self-healing using DCPD (Scheme 4) delivered through the vascular network and Grubbs catalyst dispersed in the matrix (DETA-cured DGEBA). Damage was induced using four-point bending to

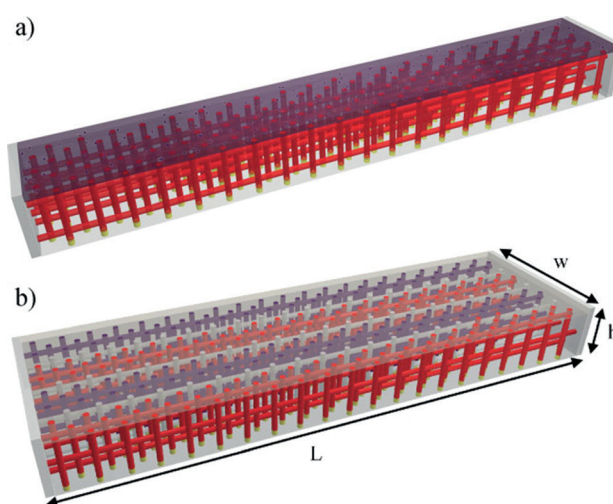


**Figure 14.** 3D printing a mould for microvascular scaffold. a) Printing ink with micronozzle deposition; b) infiltration of matrix resin into the scaffold; c) resin solidification to form the structural matrix; d) removal of fugitive ink to form a vascular network. Reproduced from Ref. [134] with permission.

initiate a single crack in the coating without damaging the underlying microvascular substrate. Fracture toughness of the coating was recovered seven times, always to approximately 50%.

As a consequence of the limitations of DCPD healing, the same system was also tested with a two-part epoxy healing system (Scheme 6).<sup>[136]</sup> The mould in this case was printed to have four independent networks to deliver the two-part healing chemicals (Figure 15).

Many of the different resins/hardener combinations tested achieved numerous healing cycles, but not in sequence;

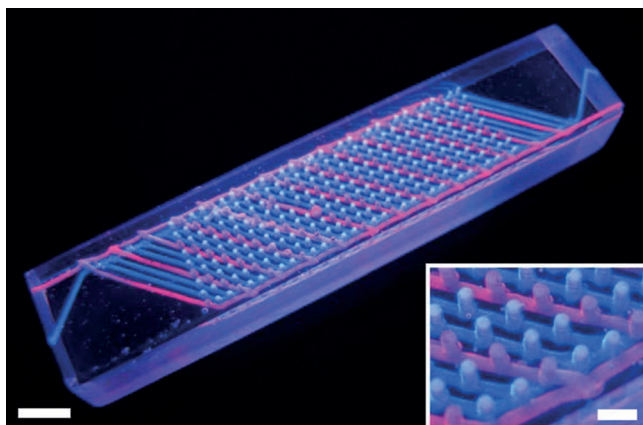


**Figure 15.** Microvascular network for a) one-component and b) two-component healing chemistry system. Reproduced from Ref. [136] with permission.

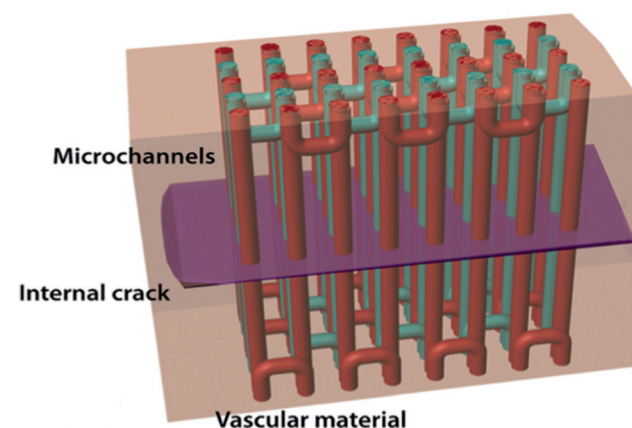
sometimes the healing simply did not work. The best case showed 16 (not successive) healing cycles, with the healing efficiency averaging above 60%.

Hansen et al. improved the mixing by using interpenetrating microvascular networks (Figure 16) and achieved over 30 continuous healing cycles, with healing efficiencies varying from close to 100% (at the beginning) to about 42% (cycle 30), by using EPON 8132 as the resin (DGEBA diluted in alkyl glycidyl ether) and EPIKURE 3046 as the hardening agent (amidoamines made from the reaction of TETA with fatty acids).<sup>[137]</sup> This two-part healing system is slow but autonomic (48 h at 30°C), can withstand different stoichiometries, and produces an epoxy with high fracture toughness, and therefore was repeatedly used for vascular healing.

The next natural step was to test internal damage that reaches the vascular system. Hamilton et al. tested multiple healing cycles of internal damage induced in a material by using double cleavage drilled compression (DCDC) fracture sample geometry.<sup>[138]</sup> In this case, up to 13 healing cycles were obtained before the formed epoxy in the crack plane obstructed the microvascular network (Figure 17).<sup>[139]</sup> The



**Figure 16.** Two independent interpenetrating microvascular networks (filled with blue and red dye) deliver each of the two-part healing system. Reproduced from Ref. [137] with permission.



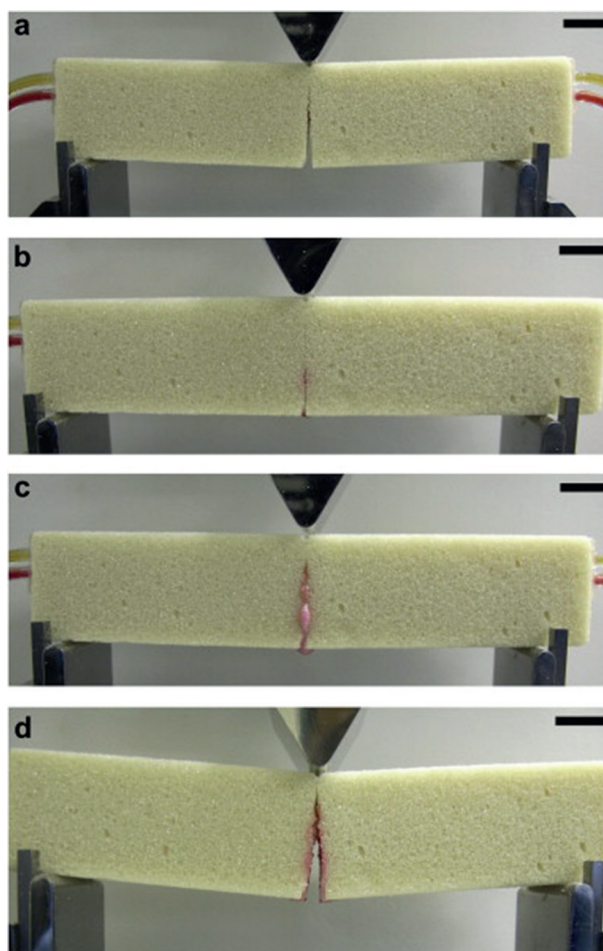
**Figure 17.** Interpenetrating network and internal crack plane used to study the self-healing of internal damage to the material and microvascular network. Reproduced from Ref. [139] with permission.

healing efficiency (applied stress necessary for crack propagation) was approximately 90% in the first cycle, but slowly decayed to about 40% in the last cycles.

Hamilton et al. also studied the effect pressurization had on the healing efficiency in internal damage by using simpler 1D channels created by exuding prepositioned nylon fibers from the matrix.<sup>[140]</sup> Improved mixing was obtained by alternating resin/hardener pumping, with healing efficiencies of nearly 100% in the first seven consecutive cycles. Fifteen healing cycles, all with over 80% healing efficiency, were demonstrated. Additionally, obstruction of the vascular system was suppressed.

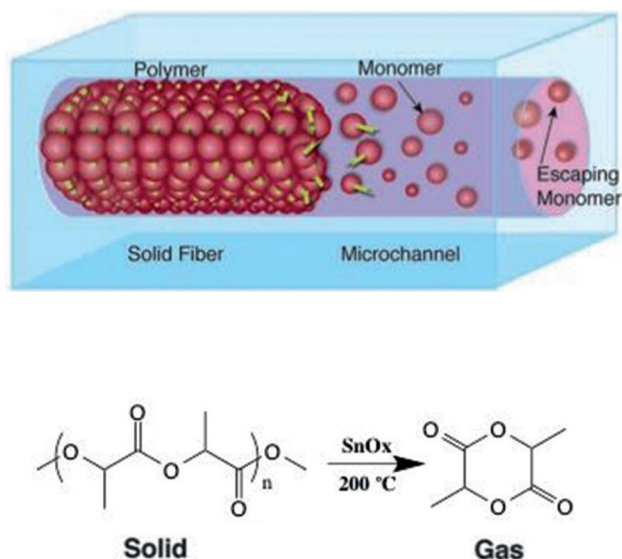
Patrick et al. proposed to solve mixing problems by using foaming chemistry. The healing system, delivered through two 1 mm diameter linear channels carved in rigid foam, consisted of a two-part foam-forming polyurethane in which heat was generated from the reaction between diisocyanates and polyols, which caused a volatile solvent to evaporate, and, thus, expand the mixture (Figure 18).<sup>[141]</sup>

The vaporization of sacrificial components (VaSC) brought a new prospect in synthetic vascular systems by allowing the creation of complex 3D vascular networks that could withstand the high-temperature curing of epoxy matrices.<sup>[142]</sup> Sacrificial poly(lactic acid) (PLA) fibers can be



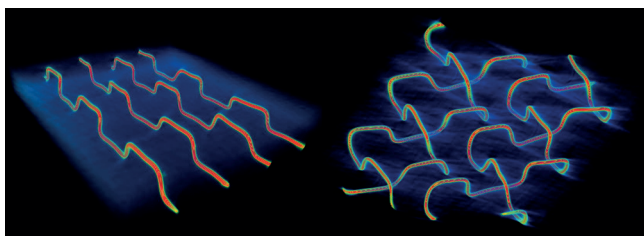
**Figure 18.** Autonomic self-healing of a rigid foam using foaming chemistry. Reproduced from Ref. [141] with permission.

woven into 3D woven glass preforms, and withstand high-temperature curing of the matrix. PLA spontaneously depolymerizes into gaseous lactide monomers at temperatures above 280 °C (Figure 19).<sup>[143]</sup> However, heating to this temperature causes degradation of the matrix. Therefore, the depolymerization temperature is lowered by embedding tin catalysts in the fibers and using vacuum to drive the equilibrium towards the monomers.<sup>[144]</sup>



**Figure 19.** Vaporization of sacrificial PLA fiber. In the presence of a tin catalyst, unzipping occurs at lower temperatures, but above the curing temperatures. Reproduced from Ref. [142] with permission.

This vascular system was recently employed by Patrick et al. to test the self-healing of internal delamination damage in fiber-reinforced composites.<sup>[145]</sup> High healing efficiencies were obtained autonomically (30 °C for 48 h) by using the two-part epoxy chemistry chosen by Hansen et al.<sup>[137]</sup> The mixing of the two parts was again raised in this study, where parallel channels provided lower healing efficiencies compared to a herringbone interpenetrating architecture (Figure 20). Three healing cycles were demonstrated with an increased healing efficiency in each cycle, but each time larger damage was needed to reach the pressurized vascular system.



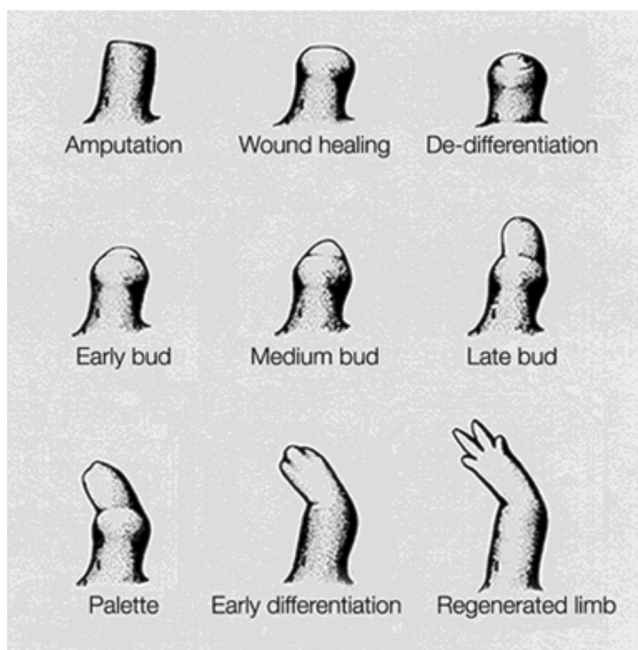
**Figure 20.** X-ray-computed microtomographic reconstructions of vascular networks filled with eutectic gallium-indium alloy for radiocontrast. Reproduced from Ref. [145] with permission.

## 5. Regeneration

### 5.1. Biological Regeneration

Regeneration is an important process in living organisms that extends over entire life spans, replacing animal and plant tissues that wear out as part of normal physiological functions and external damage.<sup>[2]</sup> Cnidarians and sponges such as corals and jellyfish can regenerate from a conglomeration of cells alone.<sup>[146]</sup> Planarians (flatworms) can regenerate their head or tail sections when severed.<sup>[147]</sup> Echinoderms such as starfish can regenerate from just one arm and the central disk.<sup>[148]</sup> In newts and salamanders, tails, legs, and eyes are regenerated.<sup>[149]</sup> Regeneration requires the organisms to maintain unspecified (stem) cells or to dedifferentiate cells to produce new specialized cells according to the necessary function (remodeling).<sup>[150]</sup> In the case of an organ amputation or large damage, self-healing occurs as described in the vascular healing. Regeneration comes as a third stage (after self-sealing and remodeling), in which unspecialized cells that are brought to or produced below the healed surface undergo an accelerated proliferation cycle that pushes the healing surface to form a bud. Concurrently, cell specialization occurs, which expands vascular and other systems, and restores function (Figure 21).

Within the human species, bone remodeling is a stress-regulated regeneration in which old or extraneous bone is removed from the skeleton through resorption and new bone is added through ossification.<sup>[12]</sup> A dynamic equilibrium between production and resorption is controlled by stress-sensitive cells (osteoblasts and osteoclasts), which are supplied by materials and nutrients from the blood.



**Figure 21.** Limb regeneration in a newt. Reproduced from Ref. [149b] with permission.



To summarize, regeneration/remodeling requires an external source of material and energy, to produce, in a controlled way, specialized material in the area of damage. This can be either a static process triggered by damage (newts) or a dynamic process in which material is constantly being renovated (bone).

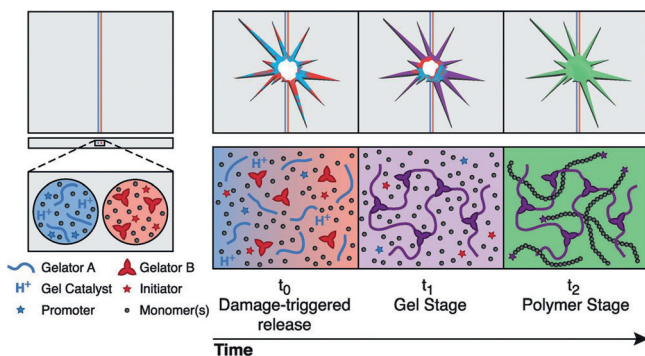
### 5.2. Challenges to Synthetic Regeneration/Remodeling

The development of synthetic regeneration/remodeling requires a combination of vascular and intrinsic healing. The vascular system provides the necessary mass transport from an outside storage to fill a large damage gap. In biological regeneration, the process is slow and the new material is either being pushed from below the skin (newts) or strongly connected to the surface (bone). The healing material needs to fill a large gap/damage and refill the original geometry, with the crack surfaces and gravity being the only moulds available. The polymerization chemicals need to adhere to the surface of the crack to deal with back pressure and gravity.

Stress-regulated polymerization and depolymerization are required to develop a dynamic system in which the material is regenerated according to its mechanical environment. Mechanochemical-triggered polymerizations were described in the intrinsic self-healing section, but an understanding of how mechanical stress alters the thermodynamic stability of polymers is necessary to develop mechanochemical depolymerization.

### 5.3. Advances towards Synthetic Regeneration/Remodeling

White et al. recently demonstrated a new approach to deal with large damage gaps.<sup>[151]</sup> Inspired by the two-step healing that occurs in response to damage to the circulatory systems of animals, the authors developed a two-stage approach: a fast self-sealing, followed by a slower polymerization to restore the mechanical properties. Self-sealing consisted of a fast gelation process, which increases the viscosity of the material and provides a weak matrix. Then, a slow polymerization occurs inside the gel matrix, which increases the stiffness of the healed material (Figure 22). This two-stage healing



**Figure 22.** Two-stage, two-part healing system for healing large gaps. Reproduced from Ref. [151] with permission.

approach allowed for gaps of tens of millimeters to be healed; all previous self-healing examples occurred with gaps on the hundred micrometer scale.

An additional advance towards stress-controlled remodeling was the demonstration of mechanically triggered depolymerization of a low ceiling temperature polymer followed by chemical repolymerization to complete a full regeneration cycle.<sup>[152]</sup> This system is different from bone, since it is not based on a dynamic chemical equilibrium, but on kinetically trapped unstable polymers. The authors proposed the use of polymers with ceiling temperatures closer to room temperature to achieve dynamic equilibrium;<sup>[153]</sup> however, the equilibrium between monomers and oligomers produces a material with low mechanical properties. Instead, the authors used high-molecular-weight polymers and paid the cost to achieve repolymerization through external energy to change the thermodynamics of the polymerization.

## 6. Summary and Perspective

The ability to adapt and heal provides longevity to all living organisms. Inspired by nature, the required chemistry, physics, and engineering tools have been developed to mimic the healing processes developed by evolution within the limitations of non-living materials.

New materials have been designed and prepared with intrinsic autonomic self-healing. A continuous challenge in this approach is overcoming the conflict between mechanical stiffness and chain dynamics, which is necessary for efficient self-healing. The recent advances made using phase-separated materials are leading the way into high stiffness materials.<sup>[54a]</sup>

Several extrinsic deliveries of healing chemicals have been engineered and tested. The generality of extrinsic healing is a big advantage, and allows for different methods to be tested in different materials. Capsule-based self-healing is very attractive both in academia (allowing for the development of different healing systems) and industry, since capsules can be easily incorporated as an additive during processing. The limitation to one healing cycle is inherent to the capsule method, but the successful healing of mechanical and other properties has been demonstrated in several materials. A single healing cycle can extend the lifetime of a material significantly, thereby reducing costs and waste.

Vascular delivery of healing chemicals is advancing towards multiple healing cycles. The development of sacrificial components allows for the preparation of complicated vasculature, which is closer to the ones found in biological systems. A big challenge still not met in synthetic systems is the restoration of vasculature during healing. Alternatively, branching and redundancy are being added to overcome clogging arising from healing events.<sup>[154]</sup>

Healing, or more precisely, regenerating large damage volumes, is arguably the hardest challenge in the field of self-healing. However, first steps were recently described, and they involve the development of more convoluted multistage chemical systems, which are closer and closer in nature to biological self-healing.

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