

Devising Synthetic Reaction Cycles for Dissipative Non-equilibrium Self-assembly

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Abstract

Fuel-driven reaction cycles are found in biological systems to control the assembly and disassembly of supramolecular materials such as the cytoskeleton. Fuel molecules can bind non-covalently to a self-assembling building block or they can react with it, resulting in covalent modifications. Overall the fuel can either switch the self-assembly process on or off. Here we take a closer look at artificial systems that mimic biological systems by making and breaking covalent bonds in a self-assembling motif. We highlight the different chemistries used so far in chronological order and comment on the pros and cons of each system. Moreover, we outline the desired traits of future reaction cycles, their fuels and waste management, and suggest two chemistries that have not been explored up to now in chemically fueled dissipative self-assembly.

Introduction

Artificial supramolecular assemblies have been used to achieve complex bio-mimetic architectures and functions with promising applications^[1] in drug delivery,^[2,3] catalysis,^[4,5] sensing,^[6,7] and molecular imaging.^[8] Until recently, man-made self-assembled structures were used either in thermodynamic equilibrium conditions or in non-dissipative non-equilibrium states (more commonly called kinetic traps).^[9,10] However, biologically occurring supramolecular systems often avoid thermodynamic equilibrium and use chemical fuels to stay in sustained non-equilibrium steady states. In the cytoskeleton, for example, nucleoside triphosphates (read: fuel molecules) bind non-covalently to proteins (or protein complexes) inducing their assembly into fibers such as actin filaments and microtubules. Continuous hydrolysis of the fuel molecules to the corresponding diphosphate analogs (read: waste products) leads to disassembly of the filaments and tubes. Lesser known is that covalent modifications are also of importance. For example, oxidation of a methionine residue in the d-loop of the actin protein structure causes disassembly of filaments.^[11] In general, in such reaction cycles, self-assembly and disassembly occur at the expense of fuel to waste conversion and heat dissipation, and hence the overall process is called dissipative self-assembly. Note that the resulting assemblies are not ‘dissipative assemblies’ or ‘dissipative structures’ in the Prigogine-sense^[12], the latter of which are emergent phenomena that occur on length scales that are much larger than that of the monomers or assemblies we will deal with in this progress report. Though seemingly wasteful in terms of energy consumption, this approach gives natural systems unprecedented adaptivity and responsiveness, while being mechanically rigid when needed by the organism. Moreover, the kinetics (and ‘kinetic asymmetry’) of the fuel-dependent steps in the reaction cycle become dominant over the

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4 thermodynamic parameters of the self-assembling units, and the overall process can even be used
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6 to store energy.^[13-15]
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10 In the past decade or so, a new generation of (supramolecular) Systems Chemists^[16] has been
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12 inspired both by the covalent as well as non-covalent modification schemes found in nature to
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14 develop artificial reaction cycles controlling assembly and disassembly processes. There are
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16 several reports which include biological elements such as enzymes,^[10,17-22] living cells,^[23,24] and
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18 DNA^[25-28], and a few others based on redox reactions,^[29-31] or transient pH-changes^[20,32-34] to
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20 create non-equilibrium conditions. These studies have uncovered new phenomena such as
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22 supramolecular oscillations and traveling fronts,^[30] reconfigurable DNA-nanotubes,^[28] or self-
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24 dividing coacervate droplets mimicking mitosis in cells^[35], which are not seen in more traditional
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26 supramolecular systems at the thermodynamic equilibrium.
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33 One direction in the field of Systems Chemistry is focussed on devising chemically fueled
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35 dissipative self-assembly without borrowing any of biologically occurring components, such as
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37 enzymes, cells, or DNA. However, as we will see in this report there is still a lack of chemistries
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39 that can make and break bonds under the same reaction conditions. Here, we will focus on systems
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41 where covalent bonds are being made and broken by synthetic means only, and hope this will
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43 inspire other chemistries to be explored in the context of dissipative self-assembly. In general, the
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45 studies reported so far incorporate chemical reaction(s) to activate building blocks to trigger their
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47 assembly, later returning back to the original state under the same reaction conditions.
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53 The desired reaction cycles can be divided into the following categories:
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57 **Cat. 1)** when spontaneous deactivation of the self-assembling molecules occurs by the solvent
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59 (e.g., hydrolysis by water);^[36-47] **Cat. 2)** where the same chemistry (catalyzed or not) is responsible
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4 for all activation and/or deactivation steps;^[48–50] **Cat. 3**) where a catalyst exclusively acts on one
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6 specific step of the reaction cycle.^[51–54] We will describe the progress in the field chronologically
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8 while mentioning the category of each example as well.
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10 11 12 **Progress so far** 13 14

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17 The first example of a chemically fueled supramolecular system by van Esch and co-workers used
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19 a methylation reaction to activate a small molecule building block (Figure 1a, Cat. 1).^[36] The
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21 authors used Dibenzoyl-(L)-cystine (DBC), which is well soluble in aqueous media at pH values
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23 above its pKa (c.a. 4.5). At least one of the carboxylic acids of DBC is converted by methyl iodide
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25 (MeI) to its corresponding methyl ester, which reduces electrostatic repulsion and leads to fiber
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27 assembly. The hydrolysis of the esters back to the acid form causes disassembly of the fibers and
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29 regeneration of DBC. The cycle can be repeated by adding further aliquots of MeI, though the
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31 response is damped due to the accumulation of waste. Five years after,^[37] the latter reaction cycle
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33 was improved by switching to dimethyl sulfate (DMS) as the methylating agent (fuel), and
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35 transient gelation could be obtained. In addition, the authors were able to regulate the lifetime of
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37 the resulting gels by the amount of fuel added. The same reaction cycle was later used to control
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39 the clustering of carboxylic acid-decorated colloids as well.^[38] This methylation/hydrolysis
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41 approach demonstrated the first chemically-fueled dissipative formation of an ‘active gel’ with a
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43 defined lifetime. These works^[36,37] opened doors to a new class of ‘life-like’ systems that are driven
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45 out-of-equilibrium by chemical fuels.
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55 In 2014, Fyles and co-authors described a chemically-fueled transport membrane system.^[48] Thiol-
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57 thioester exchange is used to ‘activate’ the mercaptan precursor (Figure 1b, Cat. 2). The resulting
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59 thioester product formed conducting channels within bilayer membranes, as could be concluded
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from the flow of ions in voltage-clamp activity experiments. The system was elegantly designed in such a way that the inactive precursor is reestablished via intramolecular lactam formation through the nucleophilic attack of the amine to the thioester.

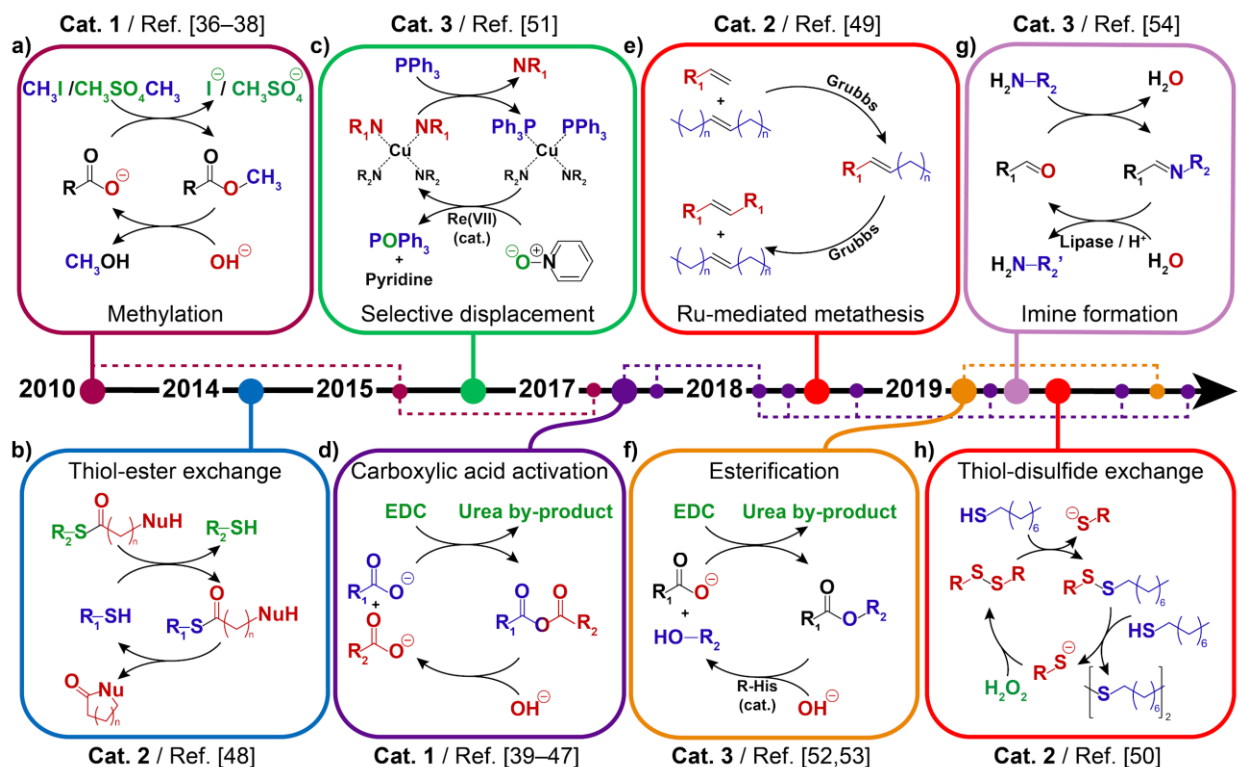


Figure 1 | Timeline of chemical reaction cycles developed so far that have been used to control the assembly and disassembly of supramolecular structures. a–h) see descriptions in the main text.

In 2015, Nitschke and co-workers reported a chemically fueled metal-templated self-assembly of supramolecular structures (Figure 1c, Cat. 3).^[51] They studied the disassembly of a Cu-based pseudorotaxane, by selective displacement of bipyridine after addition of triphenylphosphine (PPh_3). In order to recover the initial substrate, pyridine *N*-oxide and a Rhenium catalyst were used to oxidize PPh_3 to triphenylphosphine oxide OPPh_3 . With this, the authors were able to control the uptake and release of fullerene from a macrocyclic host. One of the positive attributes of this

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4 system is that the rate of disassembly can be easily controlled due to its catalytic nature and the
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6 cycle could be repeated up to six times.
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10 Boekhoven and co-authors in 2017 described a chemical reaction network driven by dicarboxylic
11 acid activation to obtain a transient anhydride (Figure 1d, Cat. 1), using the common coupling
12 agent EDC (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide).^[39] The experiments were
13 performed in aqueous buffer in which the metastable anhydride is hydrolyzed back to the starting
14 dicarboxylate. In this system, the transiently formed anhydride self-assembled into hydrogels
15 forming fibers and colloids. Tena-Solsona et al.,^[41] showed one year later the possibility of
16 achieving phase separation applying the same chemistry to fatty acids. Interestingly, they showed
17 that the anhydride product (linking together two fatty acids) phase separates into droplets and
18 consequently, the hydrolysis rate can be delayed since the anhydride is shielded from the aqueous
19 environment.^[42]
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35 Recently, Grötsch et al. extended the application of carboxylic acid activation to gold and iron
36 oxide nanoparticles.^[45] Carboxylate-terminated gold or iron-oxide nanoparticles were transiently
37 converted to N-hydroxysuccinimide esters, inducing their self-assembly. The size of the
38 assemblies could be tuned by adding different amounts of the fuel and the pathway complexity
39 depends on the preparative method. Owing to the broadly applicable functional group and the
40 easily purchased fuels, the system has been used in different examples and applications such as:
41 the dissipative assembly of macrocycles that act similarly to crown ethers;^[40] regulating the
42 assembly of luminescent silicon nanocrystals that were used to delay the delivery of silicon into
43 mammalian cells;^[43] the chemically fueled cross-linking of polymers, showing a transient increase
44 in strength of the obtained materials;^[44] the formation of dynamic vesicles that have a controlled
45 lifetime and can grow, change morphology, and be destroyed spontaneously by the addition of
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4 fuel;^[46] and the transient gel-to-gel transition from one architecture to another, of an amino-acid
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6 containing gelator.^[47]
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10 Fletcher and co-workers have demonstrated the application of two different reaction cycles in
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12 transient systems, the first one is discussed in this paragraph and the second further down. In 2018,
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14 they developed a transient self-replicating system employing a catalytic metathesis reaction
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16 (Figure 1e, Cat. 2).^[49] In a bi-phasic system, a water-soluble alkene reacts with a hydrophobic
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18 alkene through metathesis using the 2nd-generation Grubbs catalyst. The reaction product, an
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20 amphiphile, self-assembles into micelles that increase the contact area between the immiscible
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22 parts, which physically enhances the reactivity between the hydrophobic and hydrophilic
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24 substrates in an autocatalytic fashion. The surfactant then reacts with itself through cross-
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26 metathesis, to form the water-soluble/inactive thermodynamic product. If more water-soluble
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28 alkene is added, the transient cycle can be repeated. This system shows positive and negative
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30 feedback (physical), it can easily be applied to other substrates, and it uses the widely available
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32 Grubbs catalyst system. Since both the activation and deactivation reactions are mediated by the
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34 same catalyst, however, it is difficult to independently control them, thus limiting the scope of this
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36 chemistry.
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45 Recently, Das and co-workers presented a chemically fueled system where an amphiphile (C18H)
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47 comprising of an eighteen-carbon chain (C18) coupled to a histidine residue (H) was used as a
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49 substrate for esterification using 4-nitrophenol (Figure 1f, Cat. 3).^[52] This esterification step
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51 yielded a transient hydrogel that reverted back to soluble molecules upon ester hydrolysis,
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53 catalyzed by vicinal histidines. Thus the self-assembled structures create a negative feedback
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55 mechanism, which causes their own disassembly. Das and co-workers used the C18H molecule to
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57 co-assemble with a similar amphiphile with C18 stearyl and L-phenylalanine amino acid
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4 appended with nitrophenol (C18-FNP).^[53] The co-assembly of C18H and C18-FNP amphiphiles
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6 gives helical structures. The pendant phenylalanine-nitro groups linked by ester bonds (in C18-
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8 FNP) and the histidine (in C18H) are in close proximity. This allows histidine to then cleave the
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10 ester linkage causing the subsequent disassembly of the helices. The lifetime of the assemblies in
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12 the above systems depends on the cleavability of the ester bond based on the substituents of the
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14 phenol group.
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20 Recently, George and co-workers used a dynamic imine bond to form a charge-transfer surfactant
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22 that self-assembles into fibres (Figure 1g, Cat. 3).^[54] The substrate is converted from its aldehyde-
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24 containing inactive state to an amphiphile, upon the addition of an aliphatic primary amine as the
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26 chemical fuel. In this case, the deactivation of the monomer is performed enzymatically and by pH
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28 variation (tuning imine stability and reactivity). If a hydrolysable ester is present in solution (e.g.,
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30 γ -butyrolactone, β -butyrolactone or ϵ -caprolactone), the pH of the solution is decreased with a
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32 time delay, shifting the equilibrium of the imine bond towards the inactive substrates. By
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34 substituting the fully aliphatic tail of primary amine by an ester-containing alkyl chain, the
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36 presence of a lipase can hydrolyze the ester bond, rendering the building block inactive thus
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38 leading to a transient system. In both cases, the lifetime of the assembled state can be controlled
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40 by choosing the lipase concentration or by changing the amount or nature of the hydrolysable ester.
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42 The kinetics of the forward reaction can be partially controlled by using external stimuli like
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44 enzymatic pH modulation or the use of an inhibitor.
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52 The second example of Fletcher and co-workers^[50] showed a chemically fueled bi-phasic self-
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54 replicator. The used chemistry relies on disulfide exchange between a water-soluble disulfide and
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56 octanethiol, forming a surfactant (Figure 1h, Cat. 2). The thiol then reacts with the obtained
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58 amphiphile, giving a hydrophobic disulfide and inactive hydrophilic thiolate. This system shows
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4 (physical) autocatalytic and transient behavior due to the surface-active properties of the transient
5 amphiphile. However, when hydrogen peroxide is added to the solution the thiolates get
6 reactivated into water-soluble disulfides and the cycle can be repeated. When the oxidizing agent
7 is continuously supplied, steady states of the assemblies can be maintained. This system is easily
8 applicable since all the reagents and fuel are commercially available. This system, and the previous
9 one from the same group, present interesting life-like properties such as positive and negative
10 feedback and phase separation.
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22 Lee and co-workers showed a substrate driven transient assembling system,^[55] where pyridine
23 containing amphiphilic molecules self-assemble into vesicles upon addition of hydrophobic
24 substrates. The confined pocket formed by the vesicle plus the pyridine basicity can catalyze
25 chemical reactions, in this case, a nucleophilic substitution that releases hydrochloric acid as a by-
26 product. The nitrogen in the pyridine is then protonated rendering the assembly unstable, thus
27 releasing the reaction products that precipitate and can be separated by filtration. The cycle could
28 be repeated by adding potassium carbonate, which deprotonates the pyridine moiety, and the
29 original substrates. This is an interesting example of a system that performs a function (catalysis)
30 while being under kinetic control, and since the assembly is catalyzing its own destruction, it shows
31 negative feedback. The system is a substrate-driven transient system and does not have a covalent
32 modification of the self-assembling motif, so it falls outside of our three categories (see above).
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50 **Challenges and opportunities**

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54 Until recently, scientists have successfully developed reaction cycles that are applicable to widely
55 used functional groups like carboxylic acids,^[36,39] thiols,^[50] alkenes,^[49] and imines.^[54] Usually, the
56 chemical fuels that have been used, are commonly available. More complex systems,^[48,51,52]
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4 require well-designed building blocks and/or custom fuels, but they can express more sophisticated
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6 functions such as cooperative catalysis^[52] or membrane transport^[48].
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10 Compiling the different chemistries that have been discussed in this review, the greatest challenges
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12 to expanding the field can be identified. The first problem that comes to mind is the waste. By-
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14 products of the reactions hamper the ability to perform multiple cycles and therefore limit the time
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16 that out-of-equilibrium states can be sustained. Up until now only a few examples have gotten
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18 around this, either by waste removal using continuous dialysis,^[10] or in cases where the waste
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20 products are easily removable, either because they precipitate^[55] or they are in the gaseous form^[56].
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22 For future development of reaction cycles, more chemistries are needed where the waste is
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24 automatically removed by a phase change (gas/solid) or where the waste products do not interfere
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26 with the other ongoing reactions. Beyond that, reaction cycles could be coupled in tandem, where
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28 the waste of one cycle acts as the fuel for the next one.
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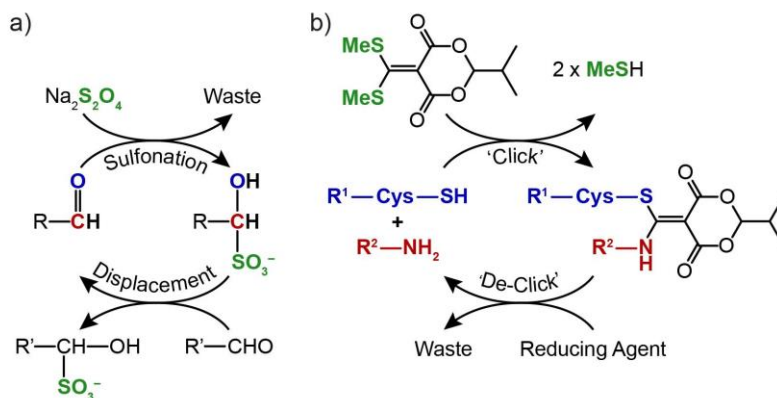
35 The chemical fuels themselves can be improved as well. The commercially available ones used so
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37 far are quite reactive, degrade slowly under the used solution conditions, and are toxic to various
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39 extents.^[36,37,39,41] One future approach could be the use of an unreactive ‘pre-fuel’ that can be
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41 converted into a more reactive species in a controlled fashion. This transformation would be done
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43 catalytically or by reacting with a second pre-fuel. Another approach would be using a catalyst
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45 that brings the substrate and fuel together to achieve high selectivity.
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51 The third important point is the control over the kinetics of the involved reaction(s). In most of the
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53 cycles designed so far, the deactivation reaction rate is solvent-mediated and hence difficult to
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55 control.^[36,37,39,41] This drawback of spontaneous deactivation is also observed in systems with
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57 carefully synthesized fuels that drive the assembly (or disassembly) of the system,^[48] or in cases
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4 where both activation/deactivation steps use similar chemistries, such as disulfide exchange or
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6 alkene metathesis.^[49,50] A promising approach to better control a reaction cycle is by using
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8 catalysis as shown by the use of a Rhenium catalyst,^[51] or the Grubbs catalyst.^[49] Ideally, the next
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10 generation of reaction cycles should use controlled catalytic reactions at each step. In this way,
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12 each contributing reaction could be individually and orthogonally controlled.
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18 Prospective systems

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21 With the plethora of organic reactions and protective group chemistries discovered so far, we could
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23 select numerous combinations to construct new reaction cycles. However, making those reactions
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25 work in tandem, is not an easy task. This is apparent from a recent example where a cycle based
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27 on redox-controlled conjugate addition and elimination chemistry was put forward.^[57] Though all
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29 individual reaction steps in the cycle were achieved, side-reactivity hampered full operation in one
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31 pot. The latter work does provide food for thought and inspiration to move towards new fuel-
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33 driven and eventually biocompatible reaction cycles, which could present interesting possibilities
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35 for non-equilibrium biomaterials. In this spirit, we present two reaction cycles that could possibly
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37 be developed into complete reaction cycles.
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4 **Figure 2 | Proposed chemical reaction cycles that could possibly be explored.** a) sulfonation/displacement
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6 chemistry, b) ‘click’/‘de-click’ chemistry.
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10 The first system currently under investigation in our group targets aldehyde groups, abundantly
11 found in nature and highly relevant to synthetic chemists (Figure 2a).^[58] Upon the addition of
12 sodium dithionite, the aldehyde moiety can be transformed into an α -hydroxy-sulfonate, which
13 triggers disassembly due to electrostatic repulsion. The original aldehyde can be recovered by the
14 addition of a more reactive aldehyde ($R'-CHO$ in Figure 2a, e.g. formaldehyde), which results in
15 a displacement reaction. To obtain transient self-assembly using the latter cycle, an aldehyde prone
16 to forming a more stable conjugate ion (in this case negatively charged hydroxy sulfonate) was
17 produced *in situ* by conversion of a pre-fuel. Practically this was achieved by the acid-catalyzed
18 degradation of hexamine into formaldehyde and ammonia. If not for the pre-fuel, dithionite would
19 directly react with formaldehyde, instead of with the self-assembling building block. This
20 chemistry is easily applicable to other gelators containing aldehyde moieties and uses cheap and
21 abundant chemical fuels.
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39 The second system uses a Meldrum's acid derivative that can reversibly cross-link a thiol and an
40 amine moiety quantitatively (cd. ‘Click’ in Figure 2b).^[59,60] Under reducing conditions the cross-
41 link is broken, which should result in the quantitative release of the respective thiol and amine
42 moieties (‘De-click’). One of the waste products would be methyl sulfide, which though smelly,
43 would escape from the system as gaseous waste. To carry out the reaction cycle in one pot, a
44 reducing agent such as dithiothreitol/cysteine could be used at low pH values to lower its reactivity
45 (without hampering the forward ‘Click’ reaction). Alternatively, the reductant could be produced
46 *in situ* using catalytic degradation of a pre-fuel allowing delayed release to be able to program the
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4 'De-click' reaction rate. This system has not been explored to achieve dissipative self-assembly
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6 yet, but has many attractive features that merit further studies.
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10 **Conclusions and outlook**

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14 Organic chemists have greatly optimized specific reaction conditions and auxiliary agents to make
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16 covalent bonds. To break those bonds again, one would typically use completely different
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18 conditions. Whereas this is of course very suitable for building up complex molecules, it is much
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20 less so when trying to design reaction cycles to control self-assembly and disassembly. Efforts in
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22 Systems Chemistry are focussed on the use of metastable or reversible bonds using a variety of
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24 approaches as we outlined here. Help is on its way from the field of chemical reaction networks,
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26 where reaction cycles are being discovered computationally.^[61,62] Using such methods novel
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28 cycles might be identified and tried out experimentally. The challenge of waste interference will
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30 remain, however, as such by-products are not necessarily incorporated in chemical reaction
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32 databases or only become problematic after significant accumulation (e.g., after several cycles
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34 have been run). In the next few years, it will be important to explore other chemistries and see
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36 what kind of life-like materials can be constructed using dissipative self-assembly (preferably
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38 under steady-state conditions). In the longer term, reaction should become biocompatible or even
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40 bio-orthogonal, so as to achieve life-like materials that can be interfaced with living matter. Such
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42 materials could have materials properties that are context-dependent^[24] and would dynamically
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44 adjust according to the environment they are placed in. A future where life-like materials bridge
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46 the gap between animate and inanimate matter could be on the horizon.
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57 **Acknowledgments**

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4 T.M.H., N.S. and S.D.P. would like to acknowledge funding from ERC-2017-STG “Life-Cycle”
5
6
7 (757910), G.J.M.F. received funding from Ministère de l’Education Nationale de l’Enseignement
8
9 supérieur et de la Recherche.

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