Angewandte Chemie

Dissipative synthetic DNA-based receptors for the transient load and release of molecular cargo

--Manuscript Draft--

Manuscript Number:	201801318R1
Article Type:	Communication
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Abstract:	Supramolecular chemistry is moving into a direction where the composition of a chemical equilibrium is no longer determined by thermodynamics, but by the efficiency at which kinetic states can be populated by energy consuming processes. Mastering this process in synthetic systems is essential for endowing materials, catalysts, drug delivery systems, with life-like properties such as adaptation, motility, and evolution. Here, we show that DNA is ideally suited for programming chemically-fueled dissipative self-assembly processes. Advantages include a perfect control over the activation site for the chemical fuel in terms of selectivity and affinity, highly selective fuel consumption which occurs exclusively in the activated complex, and a high tolerance of the systems for the presence of waste products. Finally, it is shown that chemical fuels can be used to selectively activate different functions in a system of higher complexity embedded with multiple response pathways.
Author Comments:	Dear Jens, Thank you for your letter, dated March 6, 2018, regarding our paper. We were very pleased to read the reviewers' positive comments to our manuscript! The two reviewers were enthusiastic about our manuscript and suggested publication after minor revisions. In brief we have revised portions of the manuscript in response to the comments of reviewer #1. We believe the paper has been strengthened by these changes and we hope you will find our revised paper suitable for publication in Angewandte Chemie and thank you again for your efforts on our behalf. On a final note, as for our previous correspondence, we are preparing together with a professional designer a nice image to propose as a cover picture. We will send the image by direct email as soon as it is ready (hopefully in the next days). With very best wishes, Francesco
Response to Reviewers:	The two reviewers were quite positive about our manuscript and suggested publication after minor revisions. We report below details on the changes made in response to the decision letter.

	Reviewer # 1 suggested the following changes: 1) To cite and mention a previous paper reporting another “DNA/RNA system that also is driven by energy dissipation in the presence of RNaseH”. We thank the reviewer for pointing out this interesting paper. We have added a sentence to cite it in the introduction. 2) The reviewer commented that “The word dissipative and derivatives thereof is used 32 times during the MS and there is too much focus on that aspect”. The reviewer thus suggested to “toning it down”. Also in this case we agree with the reviewer. We have revised the text to avoid over-repetition of this concept. 3) The reviewer asked some clarifications about the results presented in Figure 4b. More specifically why one system responds to non-specific fuel and why the signal noise of the other system (red) was “so pronounced compared to what was observed earlier”. We thank again the reviewer for this comment. We note that the small signal observed after the addition of fuel 2 with system 1 (blue) is likely due to non-specific interactions due to partial complementary sequences employed in this experiment. We have commented about this in the text. With regards to the noise level of the system 2 (red) we note this is likely due to the different fluorophore employed with this system that results in an overall lower signal which is thus more affected by noise. Reviewer #2 was particularly appreciative of our work and commented that this “is a very clever and elegant concept which can be applied to power any kind of DNA based machine”. The reviewer considered the work “a real breakthrough which basically provides a solution to the long standing problem of how to power DNA machines, and therefore this work will be of interest for a broad readership”. This reviewer did not suggest any revision and recommended publication as is. We believe the paper has been strengthened by these changes and we hope you will find our revised paper suitable for publication in Angewandte Chemie and thank you again for your efforts on our behalf. With very best wishes, Francesco Ricci
Section/Category:	
Additional Information:	
Question	**Response**
Dedication	
Submitted solely to this journal?	Yes
Has there been a previous version?	No
Do you or any of your co-authors have a conflict of interest to declare?	No. The authors declare no conflict of interest.

Dissipative synthetic DNA-based receptors for the transient load and release of molecular cargo**

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Abstract: Supramolecular chemistry is moving into a direction where the composition of a chemical equilibrium is no longer determined by thermodynamics, but by the efficiency at which kinetic states can be populated by energy consuming processes. Mastering this process in synthetic systems is essential for endowing materials, catalysts, drug delivery systems, with life-like properties such as adaptation, motility, and evolution. Here, we show that DNA is ideally suited for programming chemically-fueled dissipative self-assembly processes. Advantages include a perfect control over the activation site for the chemical fuel in terms of selectivity and affinity, highly selective fuel consumption which occurs exclusively in the activated complex, and a high tolerance of the systems for the presence of waste products. Finally, it is shown that chemical fuels can be used to selectively activate different functions in a system of higher complexity embedded with multiple response pathways.

Over the past decades supramolecular chemistry has permitted enormous advancements in the fields of nanotechnology,[1,2] materials science,[3,4] catalysis,[5,6] and nanomedicine.[7-10] Supramolecular chemistry exploits non-covalent interactions to form functional structures that typically reside at thermodynamic equilibrium. Although this is a favourable property for many applications, it also poses an intrinsic limitation to reproduce properties like motility, adaptation, evolution, oscillation, etc. which are characteristic of living organisms. Indeed, nature exploits chemical energy to assemble structures that are not at thermodynamic equilibrium.[11-13] This is exemplified in Figure 1, which illustrates how the high-energy state of an equilibrium reaction can be populated through alternative pathways relying on fuel consumption.

There is a strong current interest in implementing this principle in synthetic systems as it will lead to materials,[14,15] nanodevices[16] and catalysts[17] with unprecedented properties.[14,18-23] Compared to self-assembly under thermodynamic control, however, it does not require just an optimization of the thermodynamic parameters, but, more importantly, a tuning of the kinetics of the chemically distinct forward- and background reactions.[15,24-25]

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[**] This work was supported by the European Research Council, ERC (project no. 336493) (FR), by the Associazione Italiana per la Ricerca sul Cancro, AIRC (project no. 14420) (F.R.), by the Italian Ministry of Health (project no. GR-2010-2317212) (F.R.) and by the Italian Ministry of University and Research (Project of National Interest, PRIN, 2012CTAYSY) (F.R.).

Supporting information for this article is given via a link at the end of the document.

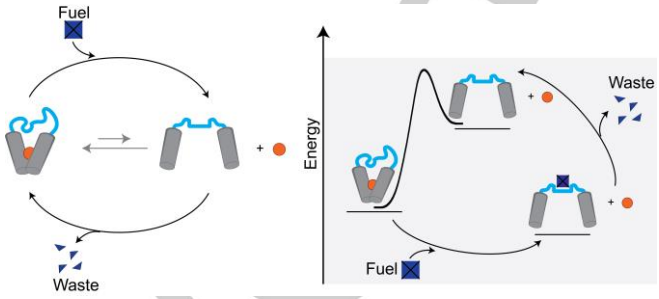

Figure 1. Non-covalent interactions between a receptor and a ligand are often described as simple thermodynamically-dominated processes in which the resulting systems reside at the thermodynamic minimum of the energy landscape. In living systems, however, chemical energy is often employed to achieve interactions that are not at thermodynamic equilibrium leading to a much more advanced way to temporally control and regulate biological processes and pathways.

Synthetic nucleic acid strands (DNA and RNA) have emerged as ideal components for self-assembly processes. The high programmability and straightforward thermodynamic prediction of the involved noncovalent interactions, together with the low cost of synthesis, has given a strong impulse to field of nanotechnology and supramolecular chemistry which is illustrated by the large number of structures, nanomachines, and materials that have been reported.[26-31] Although fuel-driven systems have been reported, mostly related to DNA-based molecular motors, walkers, or transport systems, the vast majority of examples rely on thermodynamics as the driving force for formation.[32-36]

Here, we show that *DNA* is particularly suited for designing out-of-equilibrium systems. The versatility of the systems presented here show the ease at which energy-dissipating DNA systems can be designed. This facility originates principally from the high predictability of the molecular recognition processes, which involve the fuel, but also from the high level of control that can be exerted over the kinetic processes related to fuel consumption, which is a result of the high specificity and selectivity of the enzymes used.

As a first model system we employed a clamp-like DNA-based receptor[37-39] that can recognize a specific 9-base DNA cargo through Watson-Crick and Hoogsteen interactions forming a triplex structure (Figure 2a, bottom). As the fuel we used an 18-base RNA-strand that, by binding to the loop portion of the DNA receptor, causes a conformational change that induces an opening of the triplex complex leading to the release of the DNA cargo (Figure 2a, top). Finally, as the fuel-consuming unit we employed the endoribonuclease enzyme RNase-H, an enzyme that has been already employed to control DNA-based nanodevices.[40] RNase-H is an endonuclease able to bind the RNA/DNA heteroduplex formed between the DNA-loop and the RNA-fuel and hydrolyze selectively the RNA-strand. Importantly, the enzyme acts only on RNA when it is bound to DNA, implying that fuel consumption is intimately connected to formation of the active complex.

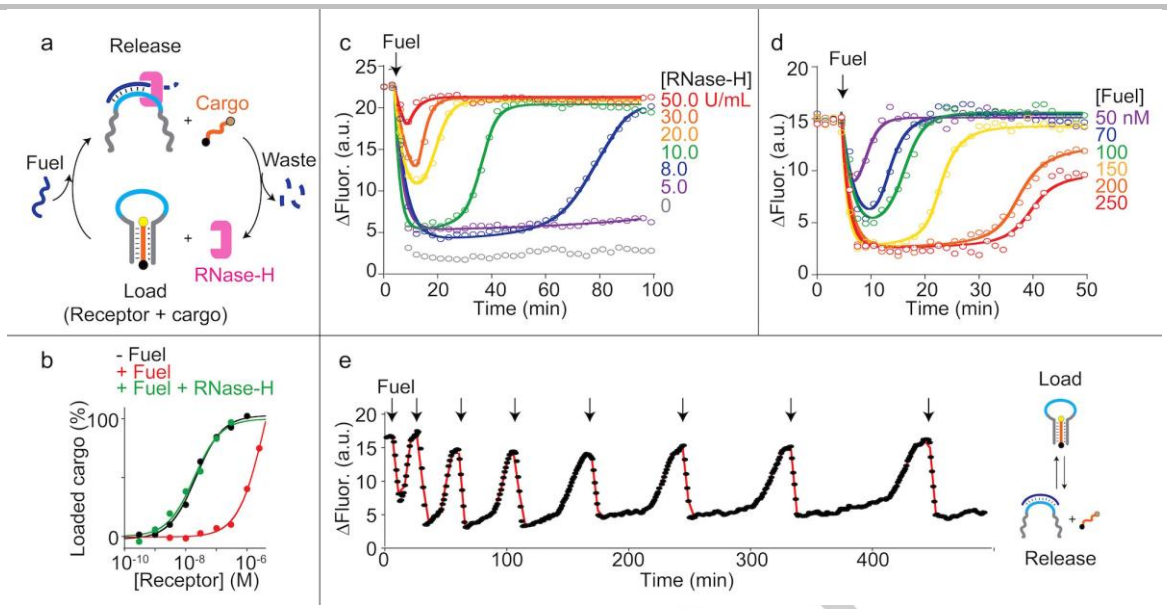

Figure 2 (a) A DNA-based receptor (grey/blue strand) for the dissipative release of a cargo (orange).**(b)** Binding curves of receptor/cargo in the absence (black) and presence (red) of equimolar concentration of the fuel strand and in the presence of both fuel and RNase-H enzyme (green). **(c)** Kinetic traces showing the transient release of the cargo (3 x 10^{-8} M) from the receptor (3 x 10^{-8} M) after addition of the fuel strand (10^{-7} M) and at different concentrations of RNase-H. Solid lines represent the best fits to the kinetic model (see text and SI). **(d)** Kinetic traces showing the release of the cargo (3 x 10^{-8} M) from the receptor (3 x 10^{-8} M) after addition of different concentration of the fuel strand and at a fixed concentration of RNase-H (25 U/mL). Solid lines represent the best fits to the kinetic model. **(e)** Kinetic traces showing the reversible transient release of the cargo (3 x 10^{-8} M) from the receptor (3 x 10^{-8} M) after sequential addition of the fuel strand (10^{-7} M) in the presence of RNase-H (25 U/mL). Experiments shown in this figure have been obtained in 10 mM Tris buffer + 3 mM $MgCl_2$ + 10 mM DTT, pH 7.0, 25°C.

This aspect is very common in naturally occurring dissipative systems, but has hardly been reproduced in synthetic systems. RNA cleavage restores the capacity of the DNA receptor to load the DNA cargo (Figure 2a, bottom). The transient load/release of the DNA-cargo can be monitored by labeling the cargo with a fluorophore/quencher pair at the two ends so that binding of such an optically labelled DNA strand to the DNA-based receptor is accompanied by an increase in fluorescent intensity while the release by a decrease in signalling.

Initially, we verified the possibility to release DNA cargo using an RNA fuel by measuring the binding affinity of the cargo for the DNA-receptor in the absence and presence of an 18-base RNA fuel strand under non-dissipative conditions (Figure 2b). As the RNA fuel causes a conformational change that inhibits triplex formation by the DNA receptor we observed a strong increase of the receptor-cargo dissociation constant by almost 3 orders of magnitude compared to that observed in the absence of RNA (K_{d_cargo} = 7 ± 2 x 10^{-9} M, $K_{d\_cargo+RNA}$ = 4 ± 1 x 10^{-6} M) (Figure 2b). This indicates that the RNA fuel is indeed a strong allosteric effector for regulating the loading and release of DNA from the receptor (Figure 2c, grey dots). Of note, in the presence of both fuel and RNase-H and after a determined period (60 min) the receptor's ability to bind the cargo was restored and we observed an affinity constant (10 ± 8 x 10^{-9} M) that is within error from the original affinity observed in the absence of the fuel (7 ± 2 x 10^{-9} M) (Figure 2b).

Under dissipative conditions, installed by the presence of RNase-H, we were able to achieve an efficient temporal control over the load/release of the DNA cargo (Figure 2c). Addition of RNA-fuel resulted in a rapid decrease in fluorescence intensity, indicating cargo release, followed over time by a gradual increase to the initial value. Control experiments using fluorescence and native PAGE electrophoresis showed that the enzyme is not able to hydrolyze the receptor/cargo complex (Figure S1-3). The time interval during which the DNA cargo is released from the receptor can be controlled both by the fuel consumption rate, which is determined by the enzyme concentration, and the fuel concentration. It was observed that upon increasing the concentration of RNase-H from 5 to 50 U/mL, with a fixed concentration of the RNA-fuel (10^{-7} M) the half-life of the cargo resident time outside the receptor is decreased from 73 to 2 minutes (Figure 2c, S4). It is noted that at high RNase-H concentration, energy dissipation occurs at such a high rate that no full displacement of all DNA cargo can be achieved. Likewise, an increase in RNA fuel concentration from 50 to 250 x 10^{-9} M at a fixed enzyme concentration (25 U/mL) caused an increase in the half-life from 2 to 38 minutes, Figure 2d, S4). The full reversibility of the transient process was demonstrated by performing multiple load-release cycles with the same system through the repetitive additions of a constant amount of fuel (10^{-7} M, Figure 2e). This experiment shows that (at least) 7 complete cycles can be formed without any significant loss of intensity. It is only noted that the kinetics of cargo re-loading slightly slow down after each cycle, which may originate from the limited stability of the enzyme over time or the inhibitory effect of waste products on enzymatic activity. Nonetheless, these results illustrate an important feature of DNA-based dissipative systems which is the high tolerance to waste products, which is a major step forwards compared to most of synthetic out-of-equilibrium systems described so far.

To gain a more complete insight into the kinetic processes involved, a kinetic model was developed and used to fit the traces collected at different concentrations of fuel and enzyme. The model takes into account the receptor-cargo and receptor-fuel binding equilibria (Figure 2b, S5-10, Supporting Info section), as well as RNA hydrolysis in the heteroduplex by the enzyme through Michaelis-Menten kinetics. Finally, since at fuel concentrations above ca. 10^{-7} M it is observed that the signal intensity does not completely return to the initial value, an interference of the hydrolysis waste products in the process has

been included (modeled as a single entity). This is coherent with the fact that RNase-H is known to produce also some oligonucleotides[41] that may compete with the fuel for binding. The minimal model is able to fit each experimental curve independently and correctly predicts the observed trends qualitatively.

An analysis of the sensitivity of the parameters reveals that the k_{cat} value, which describes the catalytic efficiency of RNase-H in cleaving the fuel, largely dictates the temporal control over the cargo release. However, both the kinetics of receptor-cargo and receptor-fuel heteroduplex formation are relevant to correctly describe the observed behaviour. The dissociation of the receptor-cargo complex controls the initial decrease in emission intensity. On the other hand the heteroduplex formation reaction becomes important after this initial phase. In the present system the fuel RNA hydrolysis, being irreversible, is always the furthest away from equilibrium and therefore has an important role in determining the speed of the entire process, just as what happens in biochemical pathways.[42] Among the reversible reactions the receptor-RNA adduct formation is kept away from equilibrium throughout the whole process, whereas the receptor-cargo equilibrium is perturbed only in the initial and final stages (see figure S11), as it adapts in a Le-Chatelier-like manner to the amount of free receptor available in the intermediate period.

An important stronghold of DNA-based out-of-equilibrium systems is related to fact that the energy dissipation pathway is highly enzyme-selective, caused by the substrate-selectivity of the involved enzyme. To demonstrate this, we employed Nt.BsmAI, which is a nickase able to recognize a specific double-strand DNA sequence and to cut only one of the two strands in a specific point. As expected, in the presence of this enzyme we do not observe any dissipative behaviour after the addition of the fuel to the receptor/cargo complex solution (Figure S12). However, the selectivity changes entirely in case we control DNA-cargo release in the above system with a DNA fuel strand (instead of RNA). In this case, Nb.BsmI, is able to dissipate energy because it recognizes and hydrolyzes selectively the DNA-fuel strand when bound to the DNA-receptor. Apart from the different enzyme used for energy dissipation, this new system bears the same characteristics as the original one in terms of reversibility and life-time control. (Figure S13-15)

From the perspective of allosteric control, the RNA-fuel causes a transient up-regulation of the concentration of DNA-cargo in the previously described system. The versatility of DNA-recognition permits equally well the design of a fuel-driven system for the transient down-regulation of the concentration of the cargo. The design is based on a stem-loop DNA-structure containing two 18-base tails at the two ends of the stem (Figure 3a). As the DNA cargo we have employed a DNA sequence complementary to the loop portion of this receptor and as the fuel an RNA strand that binds to one of the two tails of the receptor partially invading the stem portion (Figure 3a). Binding of the RNA strand (here acting as an allosteric activator) causes a conformational change that increases the affinity of the DNA-receptor for the cargo by around 1 order of magnitude (Figure S16). Also for this system we relied on RNase-H for energy dissipation, which resulted in a return of the receptor to the original stem-loop structure releasing the cargo. For this system, the release/loading of the cargo could be easily monitored by labeling the DNA-cargo with a fluorophore and the receptor with a quencher. This way association of the cargo is accompanied with a decrease in fluorescence intensity. Also this system displays an excellent performance in terms of controllability of the life time (between 7 and 34 minutes) of a single cycle by regulating either the enzyme (Figure 3b, S18) or fuel (Figure S17-18) concentration. Up to 7 load-release cycles could be easily performed with just a minor drift in the signal intensities (Figure 3c). The transient strand capture was confirmed by native PAGE electrophoresis experiments (Figure S19).

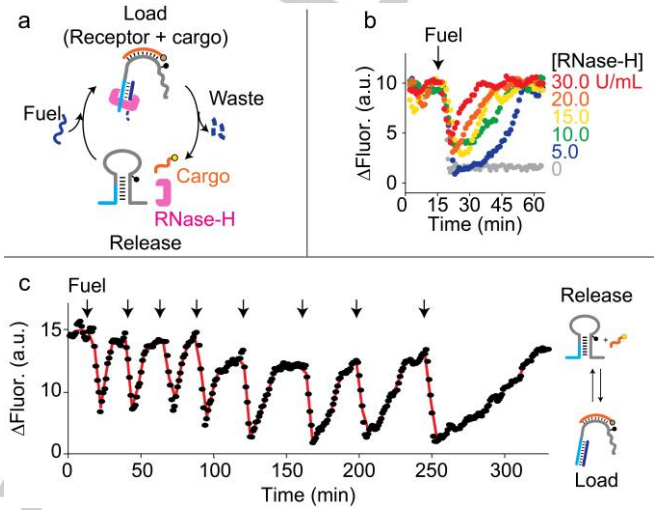

Figure 3. (a) A stem-loop receptor (grey/blue strand) for the dissipative load of a cargo (orange). **(b)** Kinetic traces showing the transient loading of the cargo (3×10^{-8} M) to the receptor (10^{-8} M) after addition of the fuel strand (3×10^{-7} M) and at different concentrations of RNase-H. **(c)** Kinetic traces showing the reversible transient loading of the cargo (3×10^{-8} M) to the receptor (10^{-8} M) after sequential addition of the fuel strand (3×10^{-7} M) in the presence of RNase-H (25 U/mL). Experiments shown in this figure have been obtained in 10 mM Tris buffer + 3 mM $MgCl_2$ + 10 mM DTT, pH 7.4, 45°C.

The systems described above illustrate the versatility of DNA as a functional material for designing out-of-equilibrium systems. Energy dissipation pathways can be selectively introduced relying on the natural selectivity of the enzymes. The systems display a high tolerance to the accumulation of waste products and a large number of cycles can be typically performed without significant signs of fatigue. Moreover, the high specificity of DNA recognition makes this material optimal to design fuel-driven dissipative systems of higher complexity. To illustrate this potential, we returned to the first example that was discussed. An important aspect of using DNA/RNA as fuel is that the activation process is subject to the same selectivity rules that govern duplex formation. Thus, the addition of a non-specific fuel having just 2-base mismatches is not able to trigger the release of the cargo (Figure S20). This implies that systems can be designed containing different fuel-loading sites, which will be transiently activated only in case the appropriate fuel is added. We illustrated this concept by designing a minimal system composed of the clamp-like receptor used earlier and an alternative receptor of the same type, but containing different cargo- and fuel-loading sites (Figure 4).

The cargo-DNA for the new receptor was labeled with a different fluorophore-quencher couple to permit a monitoring of its position independently from the original DNA-cargo. Both receptors, loaded with their respective DNA-cargo, were combined in the same solution in the presence of RNase-H as the common energy dissipating unit. Interestingly, addition of fuel 1, selective for receptor 1, resulted in the transient displacement of just cargo 1 (Figure 4, blue). On the other hand,

the addition of fuel 2 activated just receptor 2 for cargo-release (even if a minor non-specific signal is observed with system 1 probably due to partial complementary of the sequences used) (Figure 4, red). This preliminary result demonstrates for the first time that it is indeed possible to transiently activate selective functions in systems of higher complexity.

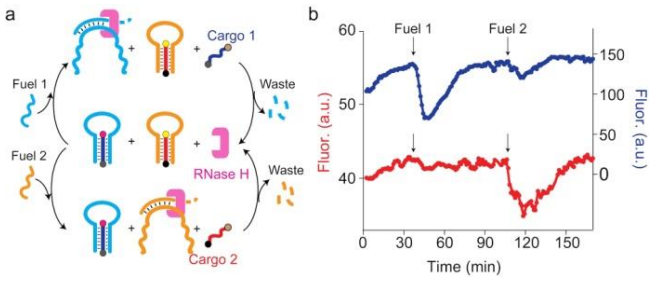

Figure 4. (a) Two different DNA-based receptors can load and release a specific nucleic acid cargo and can be controlled by a specific fuel strand. **(b)** Kinetic traces show the signals of the two different cargos (both at 3 x 10^{-8} M) from the receptor (both at 3 x 10^{-8} M) after addition of the fuel strand (5 x 10^{-8} M) in the presence of RNase-H (25 U/mL). Experiments shown in this figure have been obtained in 10 mM Tris buffer + 3 mM $MgCl_2$ + 10 mM DTT, pH 7.0, 37°C. Cargo 1 is labeled with FAM and BHQ1 while cargo 2 is labeled with Quasar670 and BHQ2.

Here we have demonstrated an efficient and versatile strategy to design synthetic DNA-based receptors that, by mimicking the real-time temporal control characteristic of allosterically-controlled biomolecular receptors and machines, can transiently and orthogonally load or release a molecular cargo under dissipative control. The examples we have demonstrated here offer several advantages compared to other out-of-equilibrium synthetic systems described to date. The use of nucleic acids also allow to choose among a wide range of available very specialized enzymes that can selectively cleave only one DNA or RNA strand in a duplex and recognize a specific sequence in the same duplex. This allows to orthogonally use different enzymes to achieve temporal control of different DNA-based receptors in a way that can hardly be achieved in other synthetic devices.

Experimental Section

Experimental details in supporting information.

Keywords: DNA nanotechnology · DNA devices · Dissipative Self-assembly · Supramolecular chemistry· Temporal control

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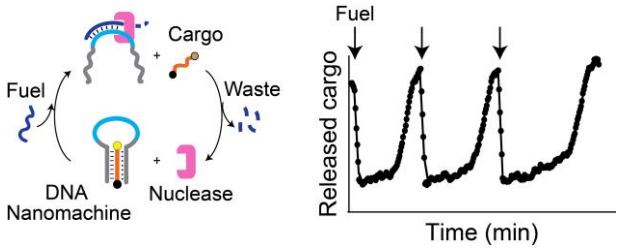

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Dissipative synthetic DNA-based receptors for the transient load and release of molecular cargo