Allosteric linkages that model the chemical cycle of a molecular motor enzyme

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Abstract

To eventually construct autonomous molecular machines that are as capable as their biological counterparts, the mechanism of allostery, which still largely cannot be explained at the atomic level, needs to be translated into a set of understandable building principles. In this study, I demonstrate a coarse-grained example of such a translation by using linkages to model the allosteric and catalytic interactions between an enzyme and its four reactants, which include a fuel, two products, and a ligand. I use the system of five linkage molecules to emulate a generic chemical pumping cycle derived from myosin, a molecular motor enzyme that is an archetype of free-energy transduction. The linkage enzyme is constructed around two binding sites - one for the fuel and product, and one for the ligand - that are negatively and allosterically coupled to one another through mutually exclusive geometries that form during binding reactions. Using stochastic simulations, I demonstrate how the design allows for a pair of allosterically triggered dissociations to alternately and cyclically take place at each binding site. The two allosteric reactions are linked together by catalysis, and enable the enzyme to be pushed through a continuous cycle of ligand binding, fuel binding, and product binding. Overall, cycling is driven by the consumption of out-of-equilibrium fuel, but it requires the reciprocating and allosterically controlled dissociations for correct operation. By showing how the chemical cycle of a biomolecular pump can be recreated with simple geometric and chemical principles that encode allosteric mechanisms, this work can help inform the development of more mechanically capable synthetic pumps and motors.

Introduction

In nanotechnology there is a long-term goal of constructing chemically-fuelled and autonomous molecular machines that actively transport small molecules over nanoscale distances [1, 2]. Inspiration for these machines comes directly from nature, where biomolecular motors and pumps play a central role in maintaining cellular activity through a variety of tasks. These tasks include muscle movement, cellular motility, cell division and many forms of analyte transport across cell membranes [3]. While a great deal has been learned about how biomolecular motors and pumps operate, it is still not clear how to construct similarly operating synthetic devices [4].

One of the most significant, but persistently opaque mechanisms governing the functionality of biomolecular machines is allostery [5, 6]. Allostery can be defined as intramolecular communication between at least two spatially separated, and often chemically distinct (non-overlapping) binding sites in a molecular machine [5, 7–9]. This non-overlapping property is what allows ATP to power different mechanical activities in different transport systems. For example, myosin uses ATP to move along actin filaments, and the sodium potassium pump uses ATP to pump sodium and potassium ions in opposite directions across a cell membrane.

Given that it functions allosterically, a general chemical question can be asked of an active transport system, preceding the question of how it produces a mechanical output, which is: how is an active transport

system able to cyclically follow a sequence of binding reactions to its fuel, fuel products and transported molecule, powered by a high concentration of fuel relative to product [10–12]? Intermolecular binding transitions bracket the hidden intramolecular transitions that take place within the cycle. And wherever mixed chemical states occur in the cycle, for which the fuel site (e.g. ATP binding site) and transport site are occupied, intramolecular transitions will occur that are by definition governed by allosteric communication [5, 13]. Any buildable model that aims to emulate the allosteric operation of biomolecular machines, needs to account for mechanisms that facilitate binding transitions in and out of these mixed states.

Recently, several theoretical works have used linkages to model how intramolecular allosteric signals are communicated from one part of a molecular machine to another [14–16]. A simple biochemical principle is assumed in these works, which is that a binding site is a multivalent entity - it is something that can be partitioned into smaller pieces which as a whole mediate binding specificity [17]. This multivalency principle is combined with a linkage phenomenon, which is that a change in distance between nodes in one part of a linkage, can cause a change in distance between nodes in another part of a linkage. Nodes are interpreted to be the flexible components in a multivalent binding site, and distance changes between nodes are interpreted to be changes in the conformation of a binding site, and thus changes to the specificity of a ligand that may bind that site. The approach is very coarse-grained and material agnostic.

In this study, I build upon this linkage-based and multivalent-binding-site approach in order to model both the intermolecular and intramolecular transitions that make up an active transport cycle. Starting with a generic active transport chemical cycle as a behavioral constraint, I use a system of interacting linkages to construct allosteric and catalytic mechanisms that result in the desired sequence of chemical changes, and show how cyclic and autonomous chemical behavior can be achieved with simple geometric and transition rate rules.

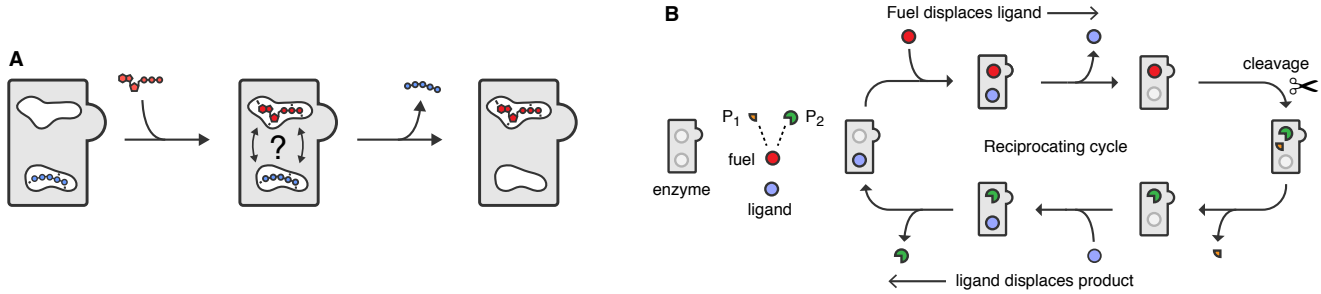

Fig. 1. Allosteric displacement and a reciprocating enzyme cycle. A, Allosteric displacement. One molecule binds (red) and kicks off another (blue), but what happens in the middle is still not understood. **B,** Reciprocating cycle. A catalytic reaction (cleavage) allows two allosteric displacements to be strung together in sequence so that a reciprocating cycle is created. Along the top of the cycle, the fuel displaces the ligand. Along the bottom of the cycle, the ligand displaces one of the products of catalysis. Cleavage is symbolized by a scissor icon.

This article is organized as follows. First, I describe how to use linkages to model a particular sequence of binding changes that very commonly takes place in motors and pumps, which I refer to as an *allosteric displacement*. In an allosteric displacement, one molecule binds and causes another already bound molecule to dissociate from an allosterically coupled site (Fig. 1A)[1]. Allosteric displacement could be considered the allosteric counterpart to a *steric* displacement, such as in DNA strand displacement [18, 19], or facilitated dissociation/competitive exchange mechanisms [20, 21], where the displaced and displacing molecules chemically overlap, and compete for the same binding site.

[1]In molecular biology this type of allosteric behavior might be described as *noncompetitive allosteric inhibition*. However, the word *inhibition*, which typically means 'to prevent from happening', fails to capture the sequence of forward (in time) binding changes I model here, hence the naming of the sequence an allosteric displacement.

By itself though, an allosteric displacement is a switch-like mechanism that is not cyclic. Hence, next, I describe how with the addition of a catalysis primitive, which allows one linkage (the enzyme) to split another linkage (the fuel) into two pieces, cyclic and reciprocal behavior can be incorporated into the system, by linking together two allosteric displacement reactions in sequence, as represented in Fig. 1B. The cycle in Fig. 1B, which is the *target* behavior, is formally extracted from the chemical cycle of a myosin monomer within the paper. It is similar to transport cycles proposed in historic papers by Terrell Hill [10, 22]. Lastly, I use stochastic simulations to show how the target transport cycle can be emulated with the linkage model, as well as *slippage*, in which imperfect coupling takes the system off the target cycle, or off-path.

Results

Allosteric displacement model

In this section, using simple geometric and rate arguments, I describe how negative allosteric communication can be designed with linkages, and describe the allosteric displacement mechanism. Consider three states that depict an allosteric binding competition between two molecules (R and B) to a third molecule M. Both R and B can make two bonds with M, but in a mutually exclusive way (Fig. 2A), mediated by an unknown structural property of M, symbolized by '?'. Mutual exclusion means that only b or f can be made but not both at the same time. On the left, B excludes R, and on the right, R excludes B. The other pair of unnamed bonds are assumed to also have this mutual exclusion relationship, but are ignored for now. Thermal energy allows the complex of three molecules to pass through an intermediate state in which both R and B are dissociated from b (Fig. 2A, middle state).

The transition rates going into the middle do not have to be equal, because b and f can have different affinities for M. As depicted in the figure, the b-b* bond is tighter that f-f* bond ($k_{\text{off-}b} < k_{\text{off-}f}$), so R can spend more time divalently bound to M than B (Fig. 2B, right), and produce an asymmetry in state occupancy. Conversely, one rate, an intramolecular binding rate (k_{uni}), is assumed to govern the two transitions out of the middle state into the side states. k_{uni} is defined to be much faster than the dissociation rates. The setup makes it highly improbable for either molecule to make two consecutive dissociations in a row, such that complete dissociation can be approached stochastically as a single jump from one weak bond.

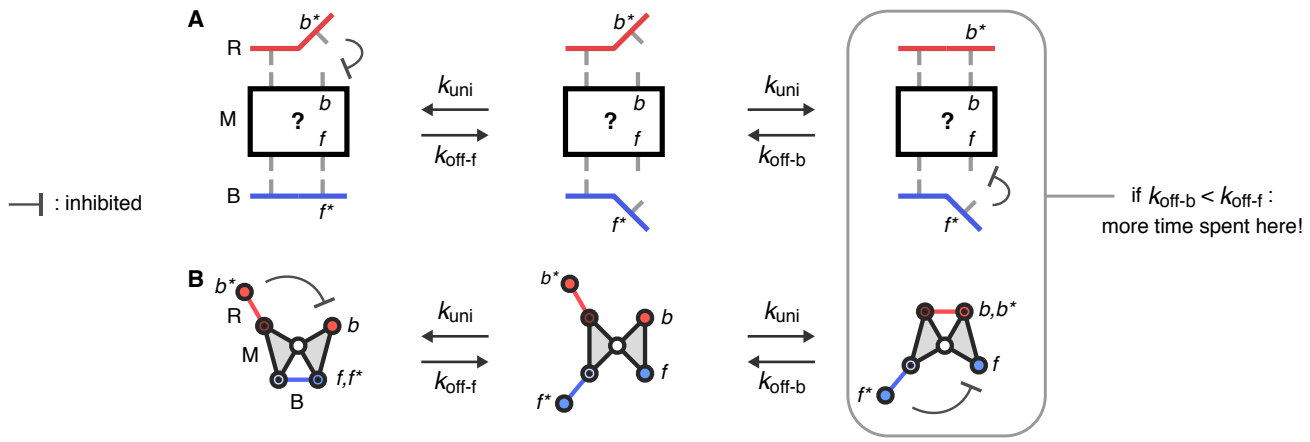

Fig. 2. Principle of allosteric exclusion and a linkage implementation. A, Principle of allosteric exclusion. These three states depict how Red (R) and Blue (B) compete allosterically for divalent binding to the Mediator (M), which mediates the interaction through some unknown geometry (symbolized by '?'). Because the competition is allosteric, the R and B binding sites are non-overlapping, and their individual interactions can have different chemical signatures, affinities, and dissociation rates. Thus, the R interaction of interest is labeled with b and b*, and the B interaction with f and f*, and the rates going into the center state, respectively, are $k_{\text{off-}b}$ and $k_{\text{off-}f}$. Broken symmetry allows more time to be spent on the right most state if $k_{\text{off-}b} < k_{\text{off-}f}$. **B,** Linkage realization of allosteric exclusion. This linkage system satisfies the exclusionary principles and rate asymmetries laid out in panel **A**. When R is bound, the linkage is pinched so that B can only make one connection with M. Conversely, when B is bound, M is pinched the other way so that R can only make one connection with M.

In Fig. 2B, a simple linkage system is shown that realizes the desired exclusion properties defined by the qualitative model in Fig. 2A. The allosteric mediator is bilaterally symmetric in shape and motion - each rigid triangle (colored grey) rotates around the central node (colored white). The two reactant molecules R and B have the same bar length, which is shorter than the distance between their complimentary nodes on the mediator in the symmetric position (middle state). Because of their shorter lengths, they pinch the mediator when they are bound at both of their nodes (side states), trapping their nodes closer together and their competitor's nodes further apart. Thus, when a competitor is bound to a single node in the pinched state, it is unable to reach its second bond, no matter what angle it assumes around the made bond. In the linkage model, allosteric exclusion has a straightforward geometric interpretation or geometric mechanism, which is that 'a bond that cannot be reached, cannot be made'.

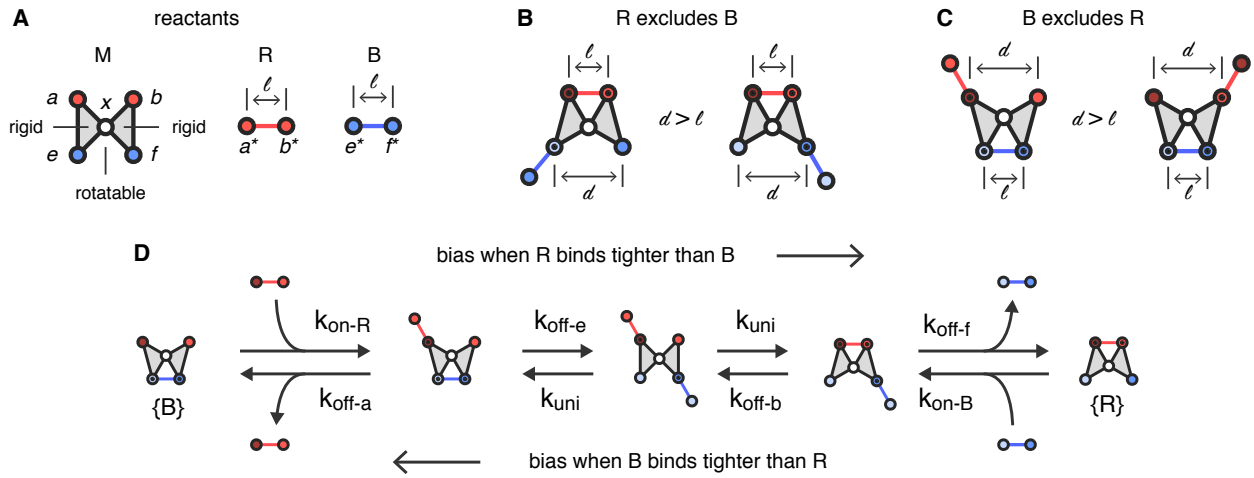

Fig. 3. Single unit mediator and allosteric displacement. A, Description of the linkage system. M is a linkage composed of two rigid triangles that can rotate around a central flexible node. R and B are the same length ℓ. **B,** R excludes B. When R is bound at both its nodes, it pinches M, preventing B from making a second bond, no matter what angle B assumes around the made bond. **C,** B excludes R. When B is bound at both its nodes, it pinches M, preventing R from making a second bond, no matter what angle B assumes around the made bond. **D,** Allosteric displacement. Going from left to right, R displaces B from the mediator. Conversely, going from right to left, B displaces R. The geometric transformations of the displacement reaction are symmetric. Only by assigning different node energies to R and B ($\varepsilon_{\mathrm{R}} = \varepsilon_{\mathrm{a}} + \varepsilon_{\mathrm{b}}$ and $\varepsilon_{\mathrm{B}} = \varepsilon_{\mathrm{e}} + \varepsilon_{\mathrm{f}}$), or different binding rates from "solution" ($k_{\text{on-R}}$ and $k_{\text{on-B}}$), is directionality created. Thus, if R and B bind at the same rate ($k_{\text{on-R}} = k_{\text{on-B}}$), R will displace B if the sum R's node energies are greater than B's ($|\varepsilon_{\mathrm{R}}| > |\varepsilon_{\mathrm{B}}|$), and B will displace R if the opposite is true. See SI 0.1 for a representation of the same network showing all possible transitions.

Fig. 3 describes in detail the components of the linkage system, its exclusion properties, and a full displacement sequence. To give a direction to the displacement reaction, each node is assigned a binding energy ($\varepsilon_{\text{node}}$, defined to be negative), so that if the absolute value of the sum of one molecule's node energies are greater than those of the other (meaning it binds more tightly), the tighter binding molecule will displace the weaker binding molecule when they are in solution at the same concentration. In the figure, assuming R and B have the same concentration and bind to M at the same rate: going right, R displaces B if $|\varepsilon_{\mathrm{R}}| > |\varepsilon_{\mathrm{B}}|$; and going left, B displaces R if $|\varepsilon_{\mathrm{B}}| > |\varepsilon_{\mathrm{R}}|$. To convert individual node energies into dissociation rates, local detailed balance can be used (See SI 0.2).

Because bound states are multivalent and connected by stepwise transitions, the system can be structured as a reaction network, through which multiple pathways can be taken to complete an allosteric displacement. As discussed later, stochastic trajectories through the reaction networks contain reversals and course changes, and thus are typically much longer than the minimal number of states required to change from one binding state to another. In Fig. 3D, five states (four transitions) are required to go from {B} to {R} (see SI 0.1 for a network representation of the allosteric displacement reaction).

Two single linkage units can be joined together to make a two-unit allosteric mediator (Fig. 4). Just as in the single-unit case, each node can be assigned a different chemistry and energy (Fig. 4, left), and just as in the single-unit case the displacement sequence takes place in a stepwise fashion (Fig. 4, right; where only one intermediate state is shown here - the complete sequence is shown later, in Fig. 7). Essentially, in the two-unit system, two one-unit displacements are taking place one-after-another - one on the left, followed by one on the right - which allows the system to pass through a transition state in which both sides are divalently bound, but by different molecules .

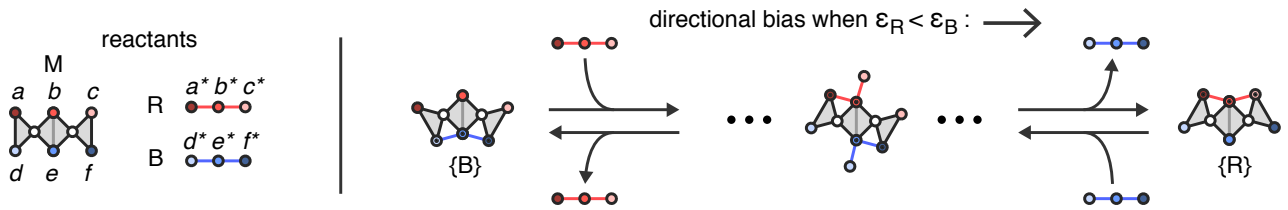

Fig. 4. Joining units together. Left, single units are joined together to make a two-unit system, where each node has its own chemical identity (a, b, c...), as in the one-unit system. Right, abbreviated displacement reaction. In going from left to right ({B} to {R}), R displaces B from the mediator, assuming that R binds more tightly than B. Only the midpoint state in the displacement reaction is shown - four states (two on each side, symbolized by: '...') are left out.

Catalysis primitive

I introduce catalysis into the model by giving one unit in the allosteric mediator the ability to cut one of the linkages that it binds into two product pieces, and in the reverse direction, join the two product pieces back together (Fig. 5). Here, the red-colored molecule is renamed the substrate (S). S is the *fuel* linkage, analogous to ATP, which is cut by the enzyme linkage into the two products (P1 and P2), which are analogous to Pi and ADP.

In the forward direction, in which S is cleaved into P1 and P2 (symbolized by a scissor icon), flexibility is introduced into the system, and in the reverse direction, in which P1 and P2 are ligated back into S (symbolized by a glue bottle icon), rigidity is introduced into the system (Fig. 5A). In the one-unit system, the cleavage reaction leads to two equally sized products, each containing a single node, whereas in the two-unit system, the cleavage reaction leads to two differently-sized products, one containing a single node, and the other containing two nodes (Figs. 5B & 5C, respectively).

The same size products in the one-unit system, versus different size products in the two-unit system results in different product stabilities (or metastabilites) in each system, and consequently different kinetic outcomes. In the one-unit system, both products easily dissociate from the enzyme, leading to the empty state ({ø}), in which nothing is bound to the enzyme (Fig. 5D). The products dissociate easily because single node associations are designed to be weak and have no way to recover once they thermally dissociate. Conversely, in the two-unit system, the two-node product P2 will remain bound in a metastable set of three states that interconvert between one another (Fig. 5E). The stability of P2 arises because intramolecular binding is much faster dissociation ($k_{\text{uni}} >>$ all k_{offs}), allowing the two-node bound state to rapidly recover after a single node dissociation event.

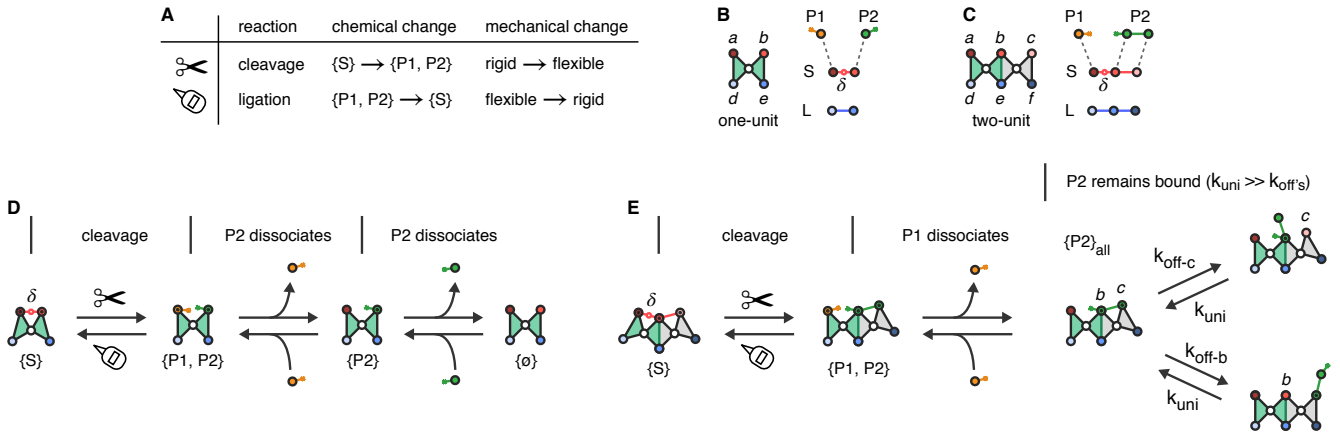

Fig. 5. Turning linkages into enzymes with catalysis. A, Defining reversible catalysis. A scissor symbolizes a cleavage reaction, which converts S into P1 and P2, and introduces flexibility into the enzyme. Conversely, a glue bottle symbolizes a ligation reaction, which converts P1 and P2 into S, and introduces rigidity into the enzyme. **B,** One-unit enzyme system. The enzyme cleaves its substrate S (red) at a special node (δ), resulting in the two product molecules P1 (orange) and P2 (green). The ligand L (blue) is left unchanged by its interaction with the enzyme. **C,** Two-unit enzyme system. Here the enzyme cleaves S into two differently sized products, where P1 has a single node, and P2 has two nodes. **D,** Catalysis and resulting decay pathway of the one-unit system. After catalysis, P1 and P2 dissociate rapidly from the enzyme because they are bound weakly at single-nodes, which have no way to recover once dissociated, and thus "diffuse" away from the enzyme. **E,** Catalysis and resulting decay pathway of the two-unit system. The decay pathway here leads to a set of three states ({P2}) in which P2 is bound metastably to the enzyme. Metastability results from intramolecular binding being much faster than dissociation ($k_{\text{uni}} >> k_{\text{off-}b}$ & $k_{\text{off-}c}$).

The significance of the catalysis reaction in the two-unit system, in regards to its operation as an autonomous machine, is that it automatically sets up the possibility for the reciprocal and allosteric displacement of P2 by ligand. The intention here is to mimic the metastability of ADP, which often stays bound to biological motors and pumps, until the requisite nucleotide exchange factor binds and displaces it from the enzyme [13, 23]. While the reciprocal displacement of P2 by L is in principle dictated by the rules established earlier, where the tighter binding molecules displaces the weaker binding molecule, an additional layer of kinetic control is required to ensure that the ligand displaces P2 allosterically, before the substrate is able to sterically displace P2, as in facilitated dissociation. This additional layer of control is discussed later in the context of the complete enzymatic cycle (Figs. 8). First, in the next section, I use the myosin monomer system to define the complete enzymatic cycle, or generic transport cycle that is the target behavior for the two-unit linkage system.

Defining a simple chemical pump using myosin

In this section I use the canonical myosin cycle to define a generic transport cycle, similar to cycles defined in older and also more recent works on transport [10, 11, 22]. Myosin is a complex enzyme that is able to produce directed motion along actin filaments, powered by ATP gradients. In cells, myosin functions as both a dimeric enzyme, as well as a more loosely coupled group of monomers. As a multimer, myosin has numerous roles in producing directed motion, including muscle movement, cellular transport and cell division, mechano-transduction, and the maintenance of synaptic plasticity in neurons [24].

While myosin often functions in teams, the canonical chemomechanical cycle of myosin, which mixes both chemical and mechanical transitions, can be defined using the monomer form of the enzyme. Starting with the canonical cycle of the monomer, I use the six chemical reactions that occur within the cycle to state three rules that summarize only the chemical behavior of the cycle (Fig. 6). By breaking one of

these rules, I show how the more simple generic transport cycle can be defined, which is the target cycle for the two-unit linkage system. By breaking the other two rules, I show how futile (slippage) cycles can be defined, in which ATP is not productively used.

The sequential and reciprocal behaviors the three rules are intended to capture are the displacement of actin from myosin by ATP, the splitting of ATP into ADP and Pi, followed by the displacement of ADP and Pi from myosin by actin (Fig. 6A). The six chemical reactions of a myosin monomer cycle are: 1, ATP binding; 2, actin dissociation; 3, hydrolysis; 4; actin binding; 5, Pi dissociation; and 6, ADP dissociation (Fig. 6B). These three rules can thus be stated as:

$$\textit{Rule 1:}\ 1 - 2 - 3$$

$$\textit{Rule 2:}\ 4 < 5$$

$$\textit{Rule 3:}\ 4 < 6$$

where '-' means 'happens directly before', and '<' means 'happens before'. *Rule 1* means that ATP binding, actin dissociation and hydrolysis should take place contiguously, before reactions 4, 5, or 6 [2]. *Rule 2* and *Rule 3* mean that actin binding should take place before Pi and ADP dissociate.

With this chemical description established, both the mechanical transitions of the lever arm and the filament structure of actin can be ignored, and the system can be graphically represented in an elementary way - with just enough detail to account for the molecular species involved (Fig. 6B). This elementary representation is used in Fig. 6C to define the target cycle. The target cycle follows *Rule 1* and *Rule 3*, but it breaks *Rule 2* ('✘ *Rule 2*'), by allowing Pi to dissociate before actin binds (Fig. 6D). As a result, the target cycle has only two allosteric displacement reactions - the first in which ATP displaces actin, and the reciprocal one in which actin displaces ADP - compared to the three that take place in the canonical cycle. While allosteric coupling is less stringent in the target cycle, ATP is still productively used because actin still has a role as a nucleotide exchange factor in the latter half of the cycle, which is critical for maintaining cyclic and ordered behavior in myosin [25].

Two futile cycles can be defined by breaking *Rule 1* ('✘ *Rule 1*'; Fig. 6C, bottom left), or *Rule 3* ('✘ *Rule 3*'; Fig. 6C, bottom right). When *Rule 1* is broken, and hydrolysis takes place before actin dissociates, the system *idles*. Idling is a non-productive use of ATP because myosin does not move from one actin site to another, though one ATP molecule is hydrolyzed. Instead, it just stays where it is, while hydrolysis and product release take place.

When *Rule 3* is broken, and ADP dissociates before actin binds, the enzyme reaches the empty state ($\{\emptyset\}$), where it is not bound by any reactant. The pathway is generally labeled as *slippage* in the figure. The empty state can be followed by either actin or ATP binding, though neither outcome is explicitly depicted. Either case results in a non-productive use of ATP, from both a chemical and mechanical standpoint: from a chemical standpoint, because actin no longer has a role as a nucleotide exchange factor; and from a mechanical standpoint, because the bipartite lever-arm stroke does not take place - which happens when Pi and then ADP dissociate while myosin is bound to actin.

It should be mentioned that the random dissociation of ADP in real myosin, leading to the empty state, is highly improbable. Tight coupling between ADP dissociation and actin binding is an important biochemical feature of a myosin enzyme that was rigorously characterized in early myosin studies [26]. I define it here because it follows from the abstract description of freely reacting components, and helps to motivate the definition of a productive enzymatic cycle (the target cycle).

The target cycle in Fig. 6C defines a generic transport cycle because its sequence interleaves steps from a driving, and driven biochemical process, where each process takes place at separate binding sites [7, 11]. Interleaving means that the driving process (ATP turnover) is reciprocally coupled to the driven

[2] Using the stronger '-' designation for *Rule 1*, instead of '<', restricts reactions 4, 5, and 6 to come after 1, 2 and 3.

process (actin binding), such that "neither reaction can be completed without the other taking place" [27]. Interleaving appears as overlap within the sequence, when both sites on the enzyme are occupied. The one additional requirement defined here, is that the enzyme is always bound by at least one molecule along its target cycle. The empty state, in which nothing is bound, is part of a futile pathway.

In the case of myosin, the chemical being pumped with the use of ATP fuel is actin. But the pumped chemical in the generic cycle does not need to be actin, and the enzyme does not need to be myosin. Actin can be replaced with any small molecule that binds to the generic enzyme in one state, and dissociates in another state. Likewise, ATP can be replaced by another molecule that is cleaved into two products. The goal of the linkage system is to reproduce the sequence of chemical changes that are defined by the generic cycle, rather than the chemicals themselves. In the next section I describe how the allosteric displacement mechanism and catalysis primitive allow this reproduction to be accomplished.

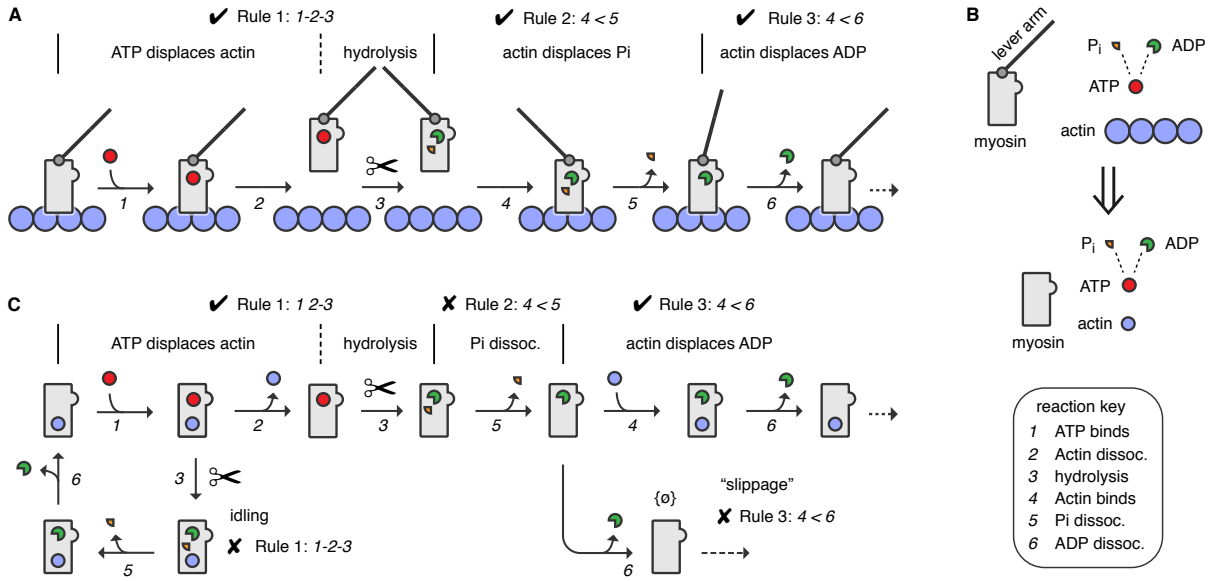

Fig. 6. The canonical myosin monomer cycle converted into a more simple chemical pumping cycle. A, Canonical myosin cycle. This cycle describes both mechanical and chemical transitions. The sequence of chemical transitions that take place can be described using three 'Rules', using the six transitions (right box) that take place in the cycle. The mechanical transitions, which are angle changes in the lever arm of myosin, occur as myosin's bound state changes. **B,** Removing the mechanical features of myosin. By removing the lever arm of myosin, and converting actin into a small ligand (as opposed to polar filament), a myosin monomer can be represented as symbolically as a purely chemical machine. **C,** The target cycle and two futile pathways. The target cycle (top row of seven states) is defined to take place when Rule 1 and 3 are followed, but Rule 2 is broken (symbolized by 'x' mark). When Rule 2 is broken Pi thermally dissociates before actin binds (5 before 4). ATP is still productively used in the cycle because actin still has a role as nucleotide exchange factor and allosterically displaces ADP from myosin. When Rule 1 is broken (bottom left), by allowing hydrolysis to take place before actin dissociation (3 before 2), the system idles, and ATP is used non-productively because myosin remains at the same actin binding site for that round of hydrolysis. When Rule 3 is broken (bottom right), by allowing ADP to dissociate before actin binding (6 before 4), ATP is also used non-productively because myosin does not reassociate with actin for that completed round of hydrolysis. This futile event is labeled generally as "slippage". Arrow notation in **A-C**: arrows depict forward transitions only.

Mapping the two-unit linkage system to the generic pumping cycle

In this section, using two figures, I map the two-unit linkage system to the generic pumping cycle, or target cycle (Fig. 7), which was defined in the previous section, and I describe the mechanisms that allow the linkage system to bias the target path over the futile paths (Figs. 8).

The target pathway

The myosin system and the two unit linkage system contain the same number of molecular species (Fig. 7A), and both systems go through the same sequence of intermolecular transitions in the target cycle (the numbered transitions in Figs. 7B & 7C). However, the allosteric displacement reactions, represented as single states in the myosin system, are expanded into a sequence of states in the linkage system that explicitly illustrate how the reaction accomplishes the requisite binding changes (Figs. 7B & 7C). In the linkage system, the allosteric displacement of ligand by substrate takes place in four steps, and the allosteric displacement of P2 by ligand (allosteric displacement 2) takes place in three steps, resulting in a thirteen state target cycle, seven more states than the myosin target cycle of six states.

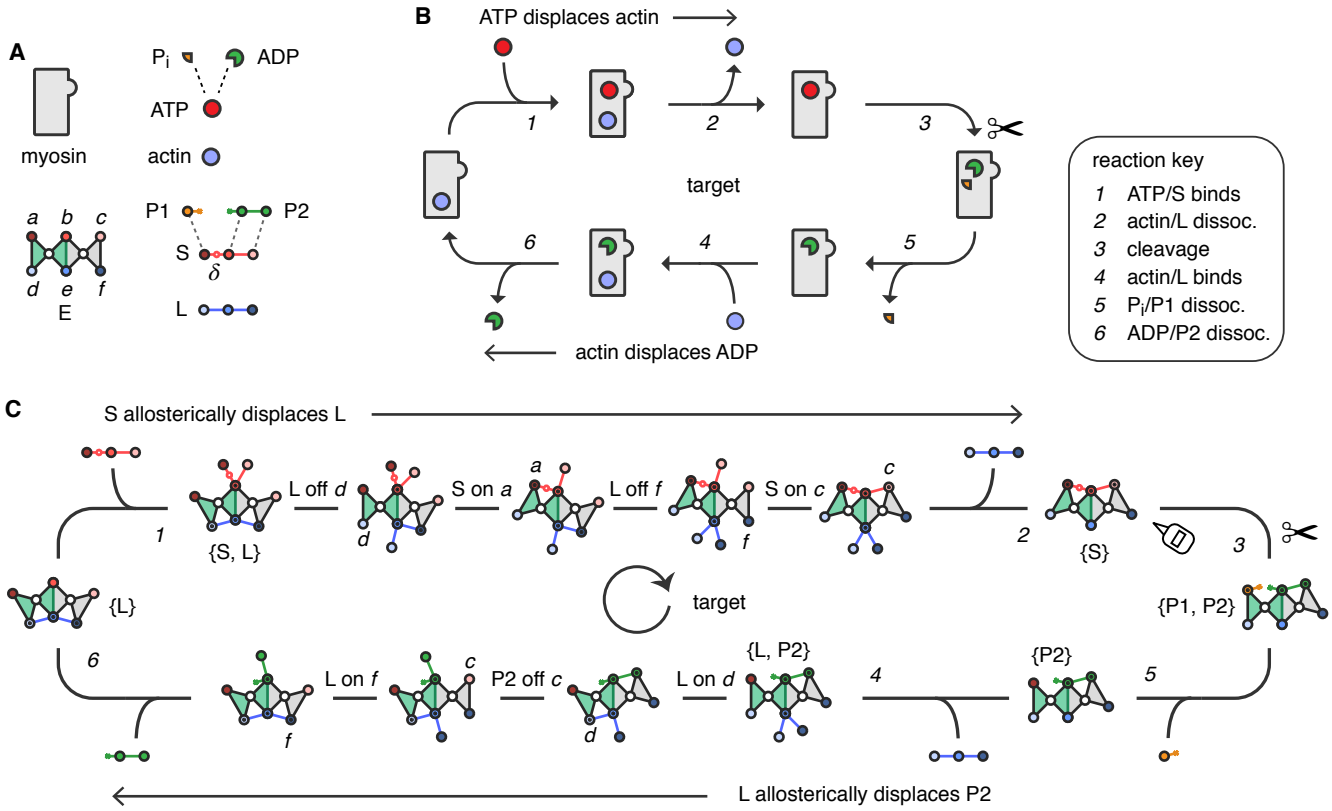

Fig. 7. Target cycle in the linkage system. A, The five molecular species of the myosin and linkage systems. **B,** A closed cycle representation of the generic pumping cycle (the target cycle) derived from myosin. Every transition (see reaction key) changes the bound state of the enzyme. The allosteric displacement of actin by ATP, and the allosteric displacement of ADP by actin, are each represented by only a single state. Arrow notation: arrows depict forward transitions only. **C,** Target cycle in the two-unit linkage system. The reaction key labels the numbered forward *inter*molecular reactions, which follow the same sequence as in myosin, while the forward *intra*molecular reactions are labeled along each transition (e.g "L off *d*"). The allosteric displacement of ligand by substrate (top of cycle), the linkage analog of the displacement of actin by ATP in myosin, is depicted in a sequence of five states; and the displacement of P2 by ligand (bottom of cycle), the analog of the displacement of ADP by actin, is depicted in a sequence of four states. Arrow notation: headless arrows depict reversible transitions.

The displacement of ligand by substrate can be thought of as two one-unit displacements (see Fig. 3D) that take place one-after-another. The first is depicted taking place on the left (green) side, during which ligand dissociates from node d and removes exclusion (Fig. 7C, allosteric displacement of L by S; 'L off d'), followed by substrate binding to node b to make a divalent association with the enzyme ('S on a'). The second is depicted taking place on the right (grey) side, during which ligand dissociates from node f and

removes exclusion ('L off f'), followed by substrate binding to node c to complete its trivalent association ('S on c'). After these steps, the ligand dissociates from node e (transition 2), leaving only the substrate bound to the enzyme. Note that in a more full network representation of this displacement reaction, other pathways are possible, including ones in which displacement starts on the right side and finishes on the left (See SI 0.3).

Following the cleavage reaction and thermal dissociation of P1 (transitions 3 & 5), the system reaches the P2-bound state. Just as in the myosin system, if P2 dissociates at this stage, before ligand binds, the system is led down a futile pathway, which is discussed in detail in Figs. 8. Along the target pathway, ligand binding leads to the allosteric displacement of P2 by ligand. Because the cleavage reaction previously removed the geometric exclusion that existed on the left side of the enzyme, the ligand is able to immediately make a second association with the enzyme on the left side, and thus bind divalently and metastably (Fig. 7C, allosteric displacement of P2 by L; 'L on d'). Divalent binding of ligand is followed by a one-unit displacement on the right side of the enzyme, where P2 dissociates from node c ('p2 off c'), and the ligand binds trivalently at node f ('L on f'). Following P2 dissociation (transition 6), the system returns to the "beginning" of the cycle, where only the ligand remains bound to the linkage enzyme.

The futile pathways

Fig. 8 describes the futile pathways, which include the idling pathway, which breaks Rule 1, and the two futile pathways emerging from the P2-bound state, which break Rule 3.

Idling takes place when ligand remains bound during cleavage (Fig. 8, turquoise pathway from the last {L, S} state). Idling is inhibited by assigning the cleavage rate to be slower than ligand's three node dissociation rates, which favors ligand dissociation over cleavage. Ligand is shown dissociating from node e, and the inequality in rates is expressed accordingly (bias i: $k_{\text{cat}} < k_{\text{off-}e}$). If idling does take place, the most likely outcome is for the system to return to the target cycle, at state {L}. This outcome is probable, because it is probable for P1 to randomly dissociate, and for ligand to allosterically displace P2 after cleavage.

Although one unit of fuel is wasted during idling, in the context of myosin, a return to the target path after an idling event can be considered more of a 'stumble' than a complete 'trip' to the system. Idling is a stumble because actin sets the coordinate system of a myosin enzyme relative to the cellular environment, and also relative to other myosin enzyme monomers when myosin is operating as a multimer. Hence, if myosin remains bound to actin after idling, progress is maintained. Likewise, when the linkage enzyme remains bound to ligand after idling, the event is defined to take place within a target cycle.

By contrast, slippage at the P2-bound state is a complete trip to the system, and sends the enzyme completely off the target cycle (Fig. 8; P2-ø, and steric displacement pathways). I distinguish between the P2-ø pathway, in which P2 randomly dissociates, leading to the empty state, and the more probable steric displacement pathway, in which P2 is sterically displaced by substrate. Both pathways break Rule 3, because P2 dissociates before ligand binds.

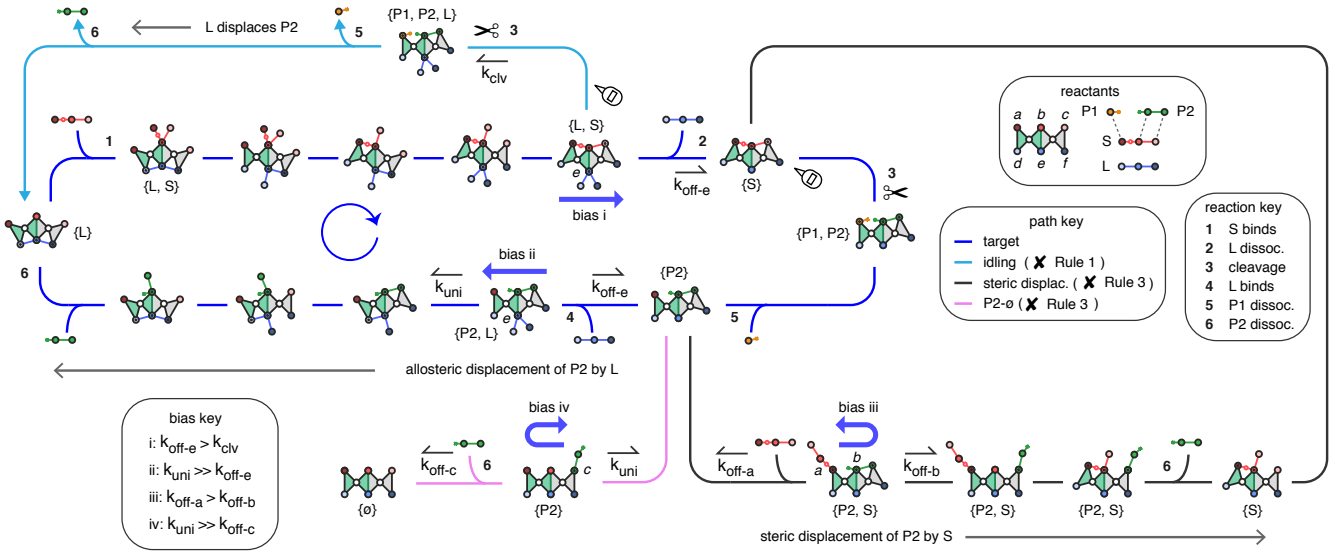

Fig. 8. Futile pathways. This figure describes the futile cycles that emerge from the target cycle at {L,S} (idling) and {P2} (P2-ø and steric displacement). Idling: Diversion at {L,S} leads to the idling pathway (turquoise), along which ligand remains bound during cleavage, or 3 comes before 2 (✘ *Rule 1*). The most probable course of events is for idling to return to the target cycle when P1 dissociates and ligand displaces P2 after cleavage. Idling is inhibited by setting the off rates for the ligand to be faster than the cleavage rate, shown for node e in the figure (bias i: $k_{\text{off-}e} > k_{\text{clv}}$). P2-ø and steric displacement: Diversion at {P2} leads to the futile pathways that violate *Rule 3* (✘ *Rule 3*), for which P2 dissociates before ligand binds, or 6 happens before 4. P2-ø (pink), along which P2 thermally dissociates leading to the empty state ({ø}), is improbable because divalent binding is stable (bias iv: $k_{\text{uni}} >> k_{\text{off-}b}$). More probable at a high concentration of substrate is the steric displacement pathway (black), along which S displaces P2 from the enzyme. Steric displacement is inhibited by setting node a, where substrate must first bind, to be weaker than node b, where P2 is bound (bias iii: $k_{\text{off-}a} > k_{\text{off-}b}$). For any single binding attempt by substrate, this assignment makes it more probable that S completely dissociates from the enzyme, than P2 partially dissociates. Thus, a return to {P2} is favored. At {P2}, the target pathway is highly favored because the ligand can immediately bind divalenty at nodes d and e, and because intramolecular binding is much faster than dissociation (bias ii: $k_{\text{uni}} >> k_{\text{off-}e}$). Arrow notation: all paths except idling, headless arrows depict reversible transitions; idling, arrows with heads depict forward transitions. Rate notation: half arrowheads above rates denote the direction to which that rate applies.

Random dissociation of P2 (P2-ø, pink path) is slow and unlikely because intramolecular binding is much faster than dissociation, allowing the divalently bound P2 to remain bound to the enzyme (bias iv, blue u-turn). If P2 does dissociate randomly and the empty state is reached, either ligand will bind and reset the system at the beginning of the cycle, or substrate will bind, leading to another futile use of fuel; futile because substrate will have been loaded on to the enzyme without having allosterically displaced ligand, which is a requirement for the productive use of fuel along the target cycle. Although neither scenario is shown in the Fig. 8, the empty state is by definition a neutral reset to the system, as nothing is bound to the enzyme, thus it makes sense that it can directly lead to the beginning (ligand binding), or to a midpoint in the cycle (substrate binding).

More than controlling for the random dissociation of P2, which is built into the multivalent dynamics of the system, kinetic control at the P2-bound state means inhibiting the possibility that substrate *sterically* displaces P2 from the enzyme, before ligand allosterically displaces P2 (steric displacement, black path). Mechanistically, the steric displacement reaction described here is related to DNA strand displacement [18, 19] and facilitated dissociation/competitive exchange mechanisms [20, 21], where the displaced and displacing molecules chemically overlap, and compete for the same binding site. In this case, S chemically overlaps with P2. In order to work properly, the system must inhibit the steric displacement pathway despite the fact that substrate is assigned to bind more tightly to the enzyme than ligand.

Steric displacement of P2 by substrate is inhibited by assigning node a, where the substrate initially binds, to have a weak affinity in comparison to node b, where P2 is already bound (bias iii: $k_{\text{off-}a} > k_{\text{off-}b}$). This assignment makes it more probable for substrate to dissociate from node a before P2 dissociates from node b, which inhibits the ability for substrate to compete for node b and bind divalenty. Thus, while substrate can still easily bind monovalently and sample the steric pathway, especially at high concentrations of substrate, the kinetic barrier makes it likely for substrate to dissociate and for the system to return to the {P2} state.

At the {P2} state, the most probable course of events is for ligand to bind rapidly and divalently, due to the left side of the enzyme being unrestricted to binding, and the assignment that intramolecular binding is much faster than dissociation (bias ii: $k_{\text{uni}} \gg k_{\text{off-}f}$). Completion of the allosteric displacement of P2 by ligand returns the system to the beginning of the cycle. In SI 0.5, I give another description of how the allosteric displacement pathway wins over the steric displacement pathway, using reaction coordinate plots and state energies.

Stochastic simulations

Overview

In this section I describe the results of the stochastic simulations, which were designed to test the performance of two-unit and one-unit linkage systems. The simulations demonstrate two main results: 1) that the two-unit linkage system favors the target cycle over the futile pathways; and 2) that the one-unit linkage system conversely favors the futile pathways over the target cycle.

To set up the simulations, I constructed chemical reaction networks for each linkage system. Each reaction network consisted of all the possible binding states that a single enzyme could make with its four reactants. For the two-unit system, one additional geometric constraint was used to generate its states. This constraint excluded states in which the substrate's or ligand's two outer nodes were bound, but not their middle node (see SI 0.6).

The chemical reaction networks were constructed in this way so that simulations could be run as 'single-molecule experiments', in the sense that the trajectories reflected the time evolution of a single enzyme as it reacted with high concentrations of substrate and ligand. Substrate concentrations ranged from 0.1 nM to 5 mM, while ligand concentrations were kept constant at 0.1 μM. Starting concentrations of P1 and P2 were set at zero for all simulations. Simulations were done with the software StochPy [28], using the Next Reaction method. While I report numbers in units of concentration, all simulations used numbers of molecules as the input, and concentrations are interpreted afterwards, using the size of the simulation box.

Tables 1, 2 and 3 give the specific parameters and rates used to perform simulations (see SI 0.7 for stochastic conversions of rates). The cleavage rate was set equal to the ligation rate to ensure that: (1) no directional bias was introduced by the catalysis interaction; and (2) cycling could be assessed as a function of reactant concentration, and the ability for the enzymes to release product. This choice was also meant to reflect the experimental observation that hydrolysis can be a highly reversible process within NTPases, with an equilibrium constant close to 1 [13, 29, 30]. The rate chosen for catalysis ($100\,\text{s}^{-1}$) is comparable to the faster rates of dissociation (weakest node interactions). In this regime, random dissociations of P1, the weakest binding product molecule, rectifies the cleavage reaction.

My workflow entailed running simulations, and analyzing trajectories using Python code that was written to determine the pathway taken by the enzyme to release each P2 molecule that was created by catalysis into solution (see SI 0.9). Because the main results rely on being able to identify the different pathways within the simulation data, I explain here in the main text how the pathways are formally defined.

Parameter	Value
Bimolecular rate constant, k_{bi}	$9 \times 10^6\,\text{M}^{-1}\text{s}^{-1}$
Concentration, c_m (m = S, P1, P2, L)	varies with m; units of M
Intermolecular binding rates, k_m	$k_{\text{bi}} \times c_m\ \text{s}^{-1}$
Intramolecular binding rate, k_{uni}	$1 \times 10^6\,\text{s}^{-1}$
Dissociation rates, $k_{\text{off-}node}$	varies with *node*; units of s^{-1}
Catalysis, k_{cat}	$100\,\text{s}^{-1}$

Table 1: Parameter definitions

Rate	Reactants	Value
$k_{\text{off-a}}$	S/P1	$250\,\text{s}^{-1}$
$k_{\text{off-b}}$	S/P2	$3\,\text{s}^{-1}$
$k_{\text{off-d}}$	L	$200\,\text{s}^{-1}$
$k_{\text{off-e}}$	L	$680\,\text{s}^{-1}$

Table 2: one-unit dissociation rates

Rate	Reactants	Value
$k_{\text{off-a}}$	S/P1	$250\,\text{s}^{-1}$
$k_{\text{off-b}}$	S/P2	$3\,\text{s}^{-1}$
$k_{\text{off-c}}$	S/P2	$680\,\text{s}^{-1}$
$k_{\text{off-d}}$	L	$680\,\text{s}^{-1}$
$k_{\text{off-e}}$	L	$200\,\text{s}^{-1}$
$k_{\text{off-f}}$	L	$680\,\text{s}^{-1}$

Table 3: two-unit dissociation rates

Defining pathways

The major reaction sequences of the system can be broken up into eight distinct blocks of behavior. These eight blocks can then be pieced together to represent the different pathways taken by the system, assuming that P1 dissociates randomly before ligand binds along these paths. A more general description is given in SI 0.9, which accurately reflects all the possible pathways that were accounted for in the final analysis. However, the simplified description given here better reflects the dominant behavior of the system. These eight behavior blocks are:

$$\begin{aligned}
\text{AD1:}\ & \{\text{L}\} \xrightarrow{1} \{\text{L, S}\} \xrightarrow{2} \{\text{S}\} \\
\text{commute:}\ & \{\text{S}\} \xrightarrow{3} \{\text{P1, P2}\} \xrightarrow{5} \{\text{P2}\} \\
\text{AD2:}\ & \{\text{P2}\} \xrightarrow{4} \{\text{L, P2}\} \xrightarrow{6} \{\text{L}\} \\
\text{idling:}\ & \{\text{L}\} \xrightarrow{1} \{\text{L, S}\} \xrightarrow{3} \{\text{P1, P2, L}\} \xrightarrow{5} \{\text{P2, L}\} \xrightarrow{6} \{\text{L}\} \\
\text{SD:}\ & \{\text{P2}\} \xrightarrow{1} \{\text{S, P2}\} \xrightarrow{6} \{\text{S}\} \\
\text{P2-}\emptyset\text{:}\ & \{\text{P2}\} \xrightarrow{6} \{\emptyset\} \\
\emptyset\text{-S:}\ & \{\emptyset\} \xrightarrow{1} \{\text{S}\} \\
\emptyset\text{-L:}\ & \{\emptyset\} \xrightarrow{4} \{\text{L}\}
\end{aligned}$$

(reactions: 1, S on; 2, L off; 3, cleave; 4, L on; 5, P1 off; 6, P2 off)

AD1 stands for allosteric displacement 1 (S displacing L), AD2 for allosteric displacement 2 (L displacing P2), and SD for steric displacement (S displacing P2).

Each pathway constructed with the blocks (futile or target) must account for the loading of substrate (r1), cleavage (r3), and release of P2 (r6), which must take place in that order, so that the P2 released can be attributed to the substrate loaded along that pathway, rather than one in a previous pathway. There are five types of pathways: (1) the target; (2) idling; (3) futile-resets; (4) futile-starts; and (5) ligand-frees.

Here, I list the dominant forms of these pathways, which are most relevant to graphically comparing the behavior of the two and one-unit systems, and to understanding the simulation results (see SI 0.9 for all forms):

target: $\overbrace{\text{AD1}}^{1,2} \rightarrow \overbrace{\text{commute}}^{3,5} \rightarrow \overbrace{\text{AD2}}^{4,6}$

futile-reset-yesS: $\overbrace{\text{AD1}}^{1,2} \rightarrow \overbrace{\text{commute}}^{3,5} \rightarrow \overbrace{\text{SD}}^{1,6}$

futile-reset-noS: $\overbrace{\text{AD1}}^{1,2} \rightarrow \overbrace{\text{commute}}^{3,5} \rightarrow \overbrace{\text{P2-ø}}^{6}$

futile-reset-complete: $\overbrace{\text{AD1}}^{1,2} \rightarrow \overbrace{\text{commute}}^{3,5} \rightarrow \overbrace{\text{P2-ø}}^{6} \rightarrow \overbrace{\text{ø-L}}^{4}$

futile-start 1: $\overbrace{\text{SD}}^{1,6} \rightarrow \overbrace{\text{commute}}^{3,5} \rightarrow \overbrace{\text{AD2}}^{4,6}$

futile-start 2: $\overbrace{\text{ø-S}}^{1} \rightarrow \overbrace{\text{commute}}^{3,5} \rightarrow \overbrace{\text{AD2}}^{4,6}$

ligand-free 1: $\overbrace{\text{SD}}^{1,6} \rightarrow \overbrace{\text{commute}}^{3,5} \rightarrow \overbrace{\text{SD}}^{1,6}$

ligand-free 2: $\overbrace{\text{ø-S}}^{1} \rightarrow \overbrace{\text{commute}}^{3,5} \rightarrow \overbrace{\text{SD}}^{1,6}$

Pathways can be thought of as being composed of two halves - a beginning and an ending half - that are either *on-target* or *off-target*. A half path is on-target if it contains the same blocks as the target sequence (AD1 or AD2), and off-target if it does not (SD, P2-ø, ø-S, or ø-L), where the commute block marks the halfway point. If either half is off-target, it is a futile pathway. Thus, the futile-resets begin on-target (AD1-commute...), but end off-target; the futile-starts begin off-target, but end on-target (...commute-AD2); and ligand-frees begin and end off-target (see SI 0.9 for more information on the pathway definitions). In the next section, the above definitions are used to describe the simulation results.

Stochastic simulation data

Simulations were performed with and without ligand, for the one and two-unit systems, over a range of substrate concentrations (Fig. 9). The goal was to look for the target and futile behaviors in each system and compare how each performs, where the one-unit system is meant to function as a control. To visualize the relevant activity, I plot the simulation data as a turnover rate for each simulation condition (Fig. 9C & 9D). The turnover rate is a measure of the rate at which P2 is released by the enzyme into "solution" - it is a general measure of enzymatic activity. The total turnover rate with ligand is further broken down into respective contributions from the five categories of pathways described in the previous section. Mini-networks for the with-ligand and no-ligand conditions, depicted using the behavior blocks, are displayed in Figs. 9A and 9B, along with a list of the pathways formed by the blocks. In Figs. 9E-9H, the blocks are additionally used to illustrate how four futile trajectories make their way back to the target cycle after having gone off-course.

Fig. 9C shows how the behavior of the two-unit system is dominated by the target cycle (blue line). At lower concentrations of substrate (below 100 nM), the target cycle occurs more frequently than occurrences of all the futile pathways summed together, verifying that the system operates as desired. At higher concentrations of substrate (above 100 nM), occurrences of the futile events begin to surpass the target cycle. As described in Fig. 8, this switch in behavior at higher concentration of substrate takes place because steric displacements of P2 by substrate become more probable at higher concentrations of substrate.

Leakage into the steric displacement pathway can be verified by comparing turnover rates for the different futile pathways that occur at high [S], and which go through the SD block. These pathways are a futile-reset-yesS, a ligand-free-1, and a futile-start-1, though...The futile-reset-yesS and futile-start pathways are coincident and occur more than the ligand-free path at [S]. Their coincidence takes place because they are jointly the shortest combined pathway back to the dominant target pathway (Fig. 9E). By contrast, occurrence of the ligand-free path requires two consecutive steric displacements to take place (Fig. 9F), which reduces its occurrence at high [S], because the target cycle and thus AD2 remain dominant at high [S].

Incidence of the futile-reset-noS and futile-reset-complete pathways, along which P2 dissociates randomly (Fig. 9G & 9H), is close to zero for all concentrations of substrate and is hardly visible on the plot, verifying that these pathways are not taken by the system.

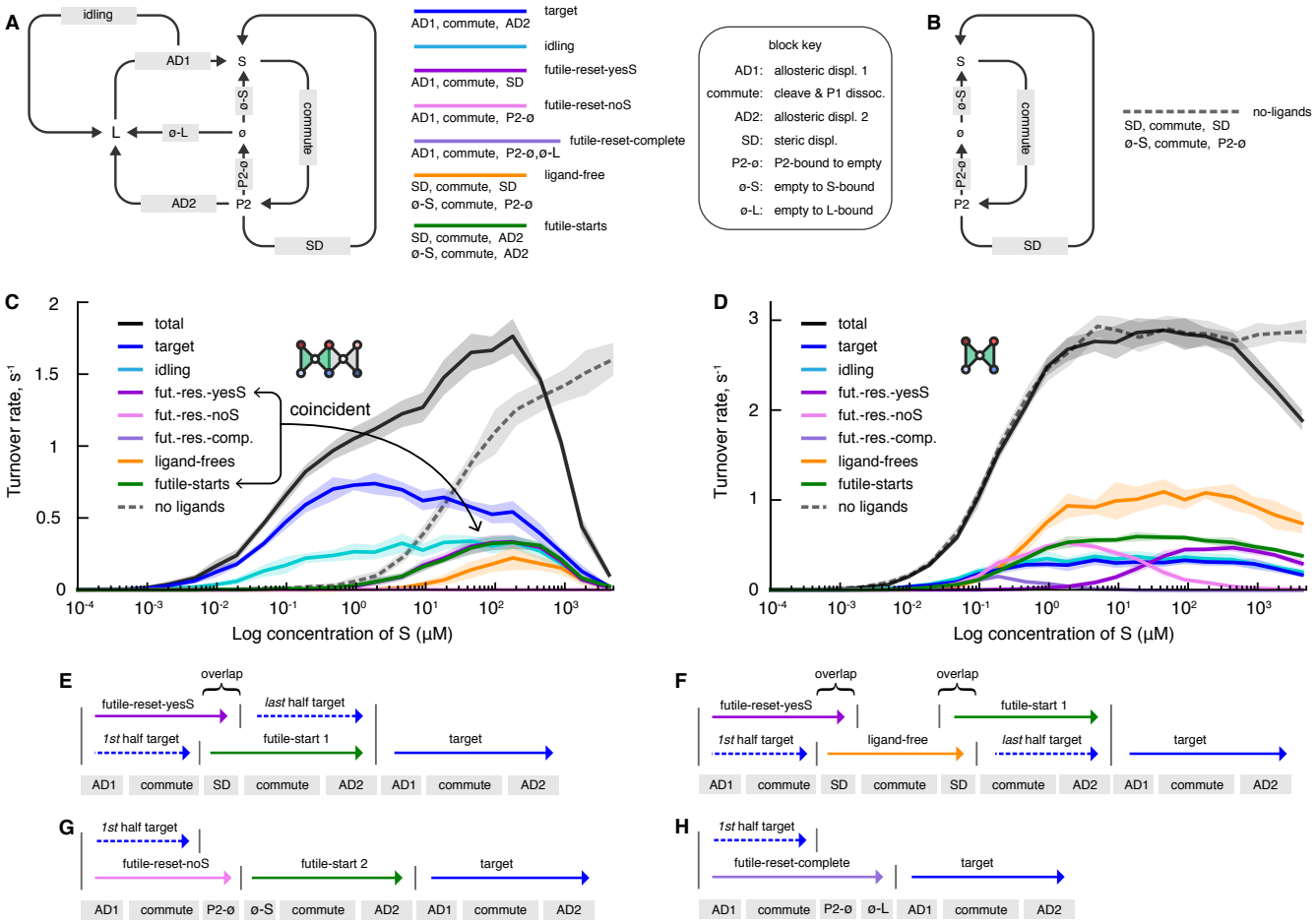

Fig. 9. Pathway decomposition from simulations and overall performance of the one and two-unit linkage systems. A, Left, With-ligand network depicted using behavior blocks. Right, Pathway legend and behavior block key. **B,** Left, No-ligand network. Right, pathway legend. **C,** Pathway decomposition in the two-unit system. Log scatter plot of the frequency with which the major pathways are taken in the two-unit system, reported by turnover rate. Substrate concentrations ranged from 0.1 nM to 5 mM and ligand concentration were held at 100 nM for all simulations. The total (black) is a sum of all the pathways, except for no-ligand (grey dashed), which reports the turnover rate for simulations done without ligand. Note that futile-start (green) and futile-reset-yesS (purple) overlap, and futile-reset-noS (light purple) remains close to zero and barely visible. Error bars are shaded areas around each scatter plot. **D,** Pathway decomposition in the one-unit system. **E,** Futile-reset-yesS back to target. **F,** Futile-reset-yesS, via ligand-free, back to target. **G,** Futile-reset-noS back to target. **H,** Futile-reset-complete back to target.

Incidence of idling (Fig. 9C, turquoise line) follows a different pattern than the other four futile pathways. Idling is less sensitive to changes in substrate concentration, and though its occurrence steadily rises with a rise in substrate concentration, it is not "activated" at certain substrate concentration as are the other futile pathways. Eventually, the incidence of idling decreases along with the overall enzymatic activity of the system, as the system reaches saturation and then inhibition, which is described next.

The total turnover rate with ligand (Fig. 9C, black line) - the summation of the target and futile pathways - increases with the concentration of substrate, until around S = 100 μM where saturation is

reached and an increase in substrate leads to a sharp decrease in enzymatic activity. Accordingly, all the contributing turnover rates also decrease at high [S]. Through a visual inspection of the trajectories and a minimal amount of analysis, I infer that the decrease begins to take place as the substrate's binding rate from solution approaches the intramolecular binding rate. As this happens, the enzyme continually saturates with one ligand and up to three substrate molecules, which makes it difficult for a single substrate to displace the ligand from the enzyme and form the cleavage complex, and consequently the turnover rate plummets.

When simulations are performed without ligand (Fig. 9C, dotted grey line), the turnover rate remains lower than the total turnover rate with ligand, until higher concentrations of substrate. At high [S], the turnover without ligand begins to increase and eventually passes the decreasing turnover rate with ligand (at S = 500 μM), but it does not reach saturation for the range of concentrations tested. Although no analysis is done to explicitly show this behavior, I extrapolate from the with-ligand data that the turnover rate without ligand increases at high substrate concentration because steric displacement of P2 by substrate occurs more at high [S] (outside path in Fig. 9B). The most significant implication of comparing the with-ligand to no-ligand condition, is that the slow rise of the turnover rate without ligand, relative to with ligand, indicates that the ligand has a large stimulatory effect on the cleavage rate of the enzyme, a point which is revisited in more detail in Fig. 10.

In contrast to the two-unit system, the behavior of the one-unit system is flipped (Fig. 9D). The one-unit system is dominated by the occurrence of the ligand-free pathway (orange), and the other futile pathways emerging from {P2}. Incidence of the target pathway (blue) is relatively low. When comparing the one and two-unit systems, it is important to keep in mind that in the one-unit system, both the steric displacement and allosteric displacement 2 sequences are not displacements as they are defined for the two-unit system (Fig. 8), as P2 is bound only monovalently to the one-unit enzyme, and thus dissociates randomly (Fig. 5D). Instead, occurrences of the two pathways simply reflect that either substrate (SD), or ligand (AD2) was bound to the enzyme when P2 dissociated.

At the lowest concentrations of substrate, incidence of all pathways, except the futile-reset-yesS pathway, rise together. The pathways reflect either the random dissociation of P2 before substrate or ligand binds (futile-reset-noS, futile-reset-complete, ligand-free and futile-start), or the binding of ligand before P2 dissociates or substrate binds (target and idling), which are all probable behaviors at low concentrations of substrate, when P2 can dissociate randomly. In particular, the random dissociation of P2 is supported by incidence of the futile-reset-noS and futile-resent-complete pathways, which are not even visible in the two-unit system.

As the concentration of substrate rises, and it binds more rapidly to the enzyme after P1 dissociates, two effects are visible on the plot. One, the brief incidence of the futile-reset-complete pathway is drowned out as it becomes more probable for substrate to bind to the empty enzyme than for ligand to bind, which is counted as a futile-start. Two, incidence of the futile-reset-noS pathway is drowned out by the futile-reset-yesS pathway, as it becomes more probable for P2 to dissociate after substrate has bound (steric displacement sequence, but not an actual displacement).

In the one-unit system, *idling* events happen slightly more than occurrences of the target cycle, whereas in the two-unit system idling events happen less than that of the target cycle (Fig. 9A & 9B, compare blue and turquoise lines). This difference further reflects better performance of the two-unit system, though the reason for this difference is not completely clear.

Saturation and inhibition also take place in the one-unit system, as can be seen in the decrease in the total turnover rate at high substrate concentration (See SI 0.8 for a calculation of the maximum turnover rate in the one-unit system). By contrast to the two-unit system, the total turnover rate without ligand tracks with the total turnover rate with ligand. The conclusion that can be made from this comparison is that the ligand has no stimulatory effect on enzymatic activity in the one-unit system. At the highest concentrations of substrate, the turnover rate without ligand flattens out and saturates, but it does not

decrease.

In Fig. 10A, I directly compare the ability for ligand to stimulate enzymatic activity in each system, using a measure called the ligand-activation-factor (A), which is defined as the ratio of the turnover rate with ligand (v_{total}), to the turnover rate without ligand(v_{noL}):

$$A = \frac{v_{\text{total}}}{v_{\text{noL}}} \tag{1}$$

For the one-unit system, A remains less than one, for all substrate concentrations (Fig. 10A, black dots), though it is difficult to see these small values of A in the scale of the plot. Values less than one reflect how the ligand inhibits rather than activates catalysis in the one-unit system. By contrast, in the two-unit system, A rises to over 50x at [S] = 0.1 μM (Fig. 10A, blue dots). The ability of the ligand to act as a switch in the two-unit system, by turning on enzymatic activity for a range of substrate concentrations, or likewise, for the enzyme to be relatively dormant in the presence of substrate alone, is consistent with the behavior of a myosin monomer, which displays strong actin-activated ATPase activity [26].

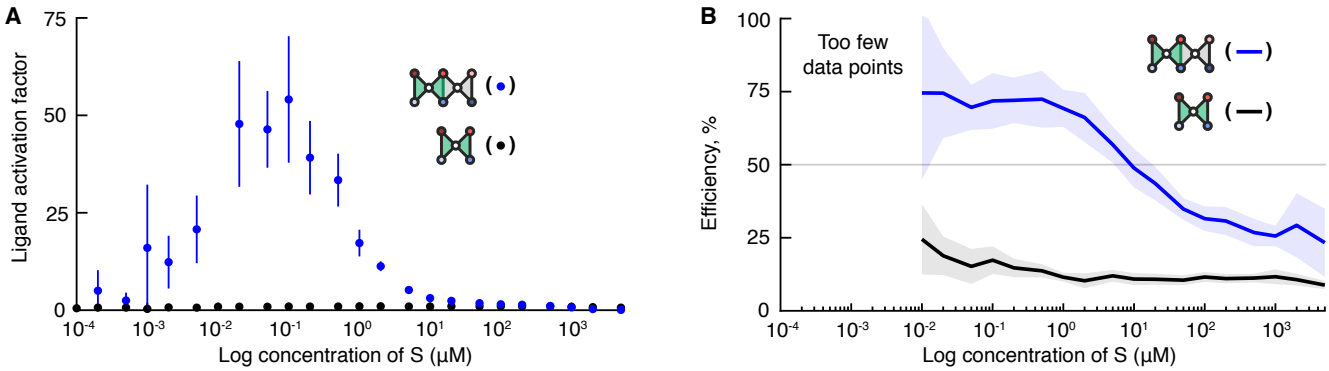

Fig. 10. Ligand activation and efficiency. A, Ligand activation. Log plot comparing ligand activation (turnover rate with ligand divided by turnover rate without ligand) in the one-unit and two-unit systems. Error bars are lines around each scatter point. **B,** Efficiency. Log plot comparing efficiencies (target rate ÷ total rate × 100) in the one-unit and two-unit systems.

In Fig. 10B, I directly compare efficiencies of the two systems. The efficiency (E) is defined as the percentage of P2's made and released by the target cycle (v_{target}), with respect to the total turnover rate with ligand (v_{total}):

$$E = 100 \times \frac{v_{\text{target}}}{v_{\text{total}}} \tag{2}$$

Fig. 10B shows that the two-unit system maintains an efficiency close to seventy percent for concentrations of substrate between 0.02 μM and 1 μM, and then falls below fifty percent above 10 μM [S]. By contrast, the efficiency of the one-unit system does not rise above twenty-five percent.

In an attempt to visually capture the cyclic and also stochastic behavior of the two-unit system, I plot thirty seconds of a simulation trajectory, where the time spent bound to the enzyme by each of the four reactants (a dwell time) is represented as a horizontal bar of color (Fig. 11). The figure is useful for visually depicting some of the "single-molecule" behaviors that cannot be understood with turnover plots, and which are relevant to understanding the operation of the two-unit system. The first is that the enzyme spends almost all of its time bound to at least one molecule, as can be seen in the thirty seconds shown, except for one instance in which a frnS & fs take place (between cycles 8 and 9). And, these bound states occur mostly within consecutive target cycles. Overlap between consecutive target cycles, which

takes place when ligand displaces P2, is also visible (see cycles 11 to 13 for example). Most of the target cycles overlap with their preceding and trailing target cycles, except for 1, 9, and 11.

The second behavior is that idling, which is the most common futile pathway taken at this concentration of substrate, is visible as a "stumble" rather than complete trip to the system. In all incidences of idling, except one, the ligand molecule that is bound at the beginning of the idling event, and which remains bound after the event, defines the beginning of a target cycle. This start to a target cycle means that these idling events occur within those target cycles. For example, the first two idling events that are labeled in the plot, both take place within target cycle 2. The exception to this takes place between the end of target cycle 10 and beginning of 11, where the ligand molecule bound dissociates during the idling event (Fig. 11, see idling*).

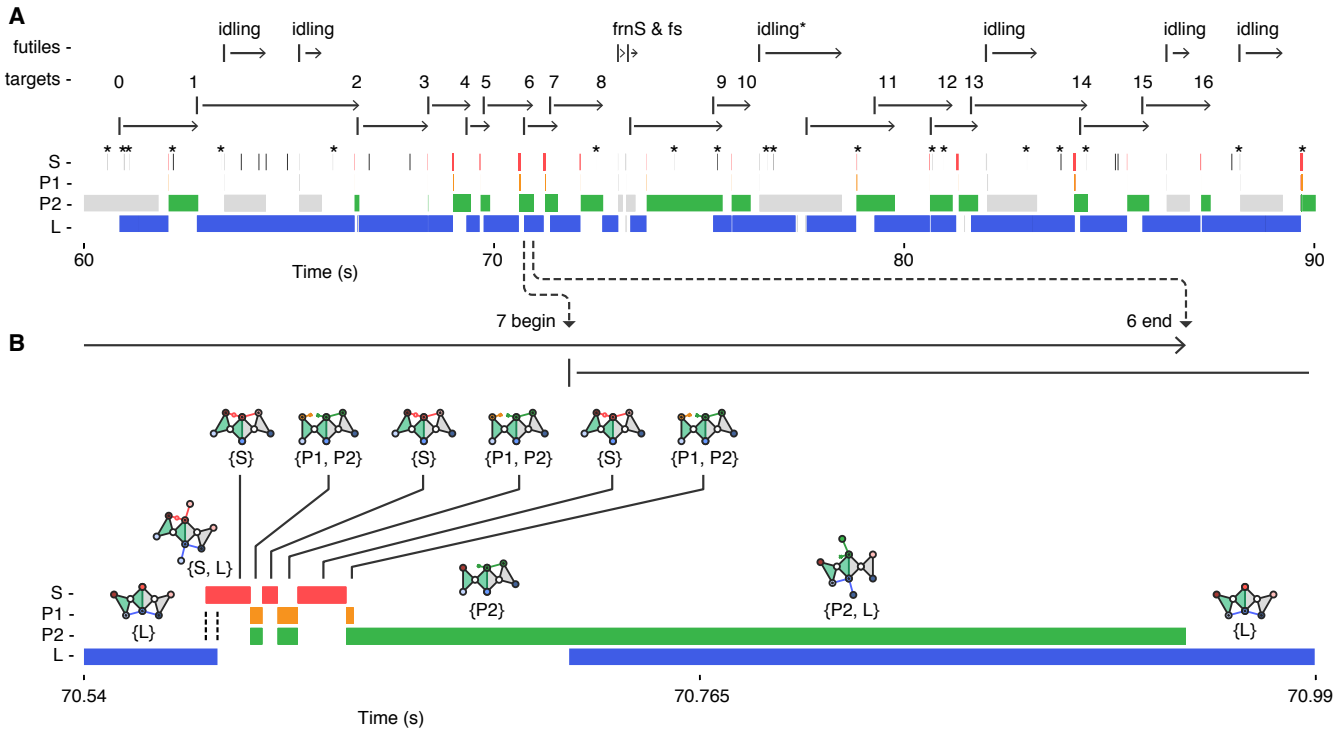

Fig. 11. Dwell time plot of a stochastic trajectory, and the reversibility of catalysis. A, Thirty seconds of a ninety second trajectory done at 100 nM S and 100 nM L. The time spent bound to the enzyme by each reactant is represented as a horizontal bar of color (S, red; P1, orange; P2, green; and L, blue). Bound states within futile events are colored with grey bars. Spurious substrate and ligand binding events (which are very short lived) are labeled with stars ('∗'). At the top, the arrows going from left to right span the duration of futile events (idling, frnS and fs) and target cycles (numbered from 1 to 16). Numbers are shown above arrowheads, marking the endings of the target cycles, while vertical bars mark the beginnings. Target cycle arrows are staggered because consecutive target cycles overlap. Note that target cycles start at ligand binding, and end at P2 dissociation - most clearly seen in cycle 11, as it does not overlap with cycle 10. **B,** Reversibility of catalysis. A zoom (∼70x) of the end portion of target cycle 6 and the beginning of cycle 7, which spans 0.45 seconds of the trajectory. Bound states are represented above by the most connected linkage state in that set. Here, it can be seen how three consecutive cleavage events (red to orange-green overlap) and ligation events (orange-green overlap to red) take place before P1 dissociates (orange-green overlap to green) and rectifies the system. Although not visible in panel **A**, cycles 4 and 14 also display reversible catalysis.

The third behavior is that the plot generally gives a sense of dwell times at peak performance of the system. The enzyme spends most of its time bound to ligand, P2 or both, and a comparatively little amount of time bound to substrate. Accordingly, allosteric displacement of ligand by substrate (overlap

of red and blue) is rapid relative to allosteric displacement of P2 by ligand (overlap of green and blue). A single instance of this comparison is easily seen in Fig. 11B, which is a 70x zoom of target cycle 6. The dwell time pattern is consistent, though a systematic analysis was not carried out in this study.

The fourth and most mechanistically significant behavior, visible only in Fig. 11B, is the reversibility of the catalysis reaction. In the zoomed in view of cycle 6, the cleavage reaction ({S} → {P1, P2}; red to orange-green overlap) is twice reversed by a ligation reaction ({P1, P2} → {S}; orange-green overlap to red), until P1 dissociates after the third cleavage reaction to rectify the reaction. Although not magnified and thus not visible, cycles 4 and 14 also display reversible catalysis. These cycles, which ultimately go forward despite reversing at the catalysis stage, reflect how the direction of the catalysis reaction is controlled by the respective stabilities of the species bound at either end of the cleavage and ligation reactions (S vs P1 and P2), rather than the rate of cleavage vs ligation, which are set equal to one another.

Discussion

With the linkage system, I demonstrate three mechanisms (allosteric displacement, a catalysis primitive and kinetic control) that allow autonomous cycling to take place in an abstract model of a simple chemical pump. Allosteric displacement, the first mechanism, demonstrates how downhill binding can allosterically drive uphill dissociation from a third molecule in order to exchange the binding partner. If the exchange process is looked at as one large energetic barrier, then the displacement reaction overcomes this barrier by splitting the exchange into a sequence of small thermally triggered mechanical sub-steps [31, 32](SI Fig. 15). By the end, the incoming molecule converts the initially multivalently bound outgoing molecule into a single weak association. Only rebinding reactions of the outgoing molecule are inhibited during the allosteric displacement sequence, while dissociations happen freely, which echoes the supposition that "chemical energy is used to prevent backward motion rather than to cause forward motion" in Brownian motors [6]. In this case, rebinding of the outgoing molecule is "backward motion", and dissociation is "forward motion".

Because a single allosteric displacement reaction is a switch-like event that cannot alone drive a cyclic process, I introduced a catalysis primitive. The primitive reverses the thermodynamic "current" of the system, by allowing a second downhill allosteric displacement to take place that goes in the opposite direction relative to the binding sites and their bound state. Catalysis is defined to be an energetically symmetric reaction: the rates for cleavage and ligation are set equal to one another; and the same bonds with the same energies are made before and after cleavage. The important transformation that takes place during catalysis is the splitting of substrate into two molecules, which introduces flexibility, and allows the two products to act as energetically independent entities inside of the enzyme. This independence allows P1 to randomly dissociate, and places the affinity of a stably bound P2 lower than that of the ligand, allowing ligand to allosterically displace P2 and return the system to the start of the cycle. Hence, the catalysis primitive provides a clear interpretation of how the equilibrium constant of catalysis can be one [13, 33], but still trigger forward progress by acting as a geometric gateway.

Kinetic control over competitive binding, the third mechanism demonstrated, allows the ligand to allosterically displace P2 before the substrate sterically displaces P2. The important point here is that the ligand wins because it binds to the linkage enzyme at a distinct set of bonds that do not overlap with the substrate or P2, despite binding more weakly to the enzyme than substrate. This orthogonality allows the ligand to take advantage of the enzymes two mechanical degrees of freedom and bind divalently, and from this metastable state allosterically displace P2 from the enzyme. By contrast, the steric displacement of P2 by substrate is a slower and more reversible process, because the substrate can initially bind only monovalently while it waits for P2 to dissociate. A question that arises is whether allosteric and steric displacement [20, 21] pathways might jointly occur and compete in sufficiently complex biological enzymes

that rely on exchange factors to remove product, which often bind at allosteric sites.

The linkage system demonstrates two levels at which the fuel and ligand processes are interleaved with one another: one at the intermolecular level that tracks with chemical changes, in which binding triggers dissociation, in a see-saw like manner; and a second at the intramolecular level that tracks with chemomechanical changes at multivalent sites, in which dissociation must precede binding, in order to go forward. With this dense arrangement of transitions the enzyme is always occupied during its productive cycle, and the empty state is considered off-path. This always occupied condition conforms to many experimental descriptions of pumps and motors in which the empty state is also considered "off path". Examples include myosin, kinesin, and the F1 motor.

In addition to theoretical questions, the usefulness of the linkage model to engineering more functional synthetic motors is that multiple chemistries can be potentially be used to construct linkage-like structures, including DNA and RNA nanotechnologies [34–37], rotaxane/catenane chemistry [4], and peptide chemistry [38], or a combination of chemistries. While nucleic acid nanotechnologies are currently the most developed for this application [39–43], protein structural design is rapidly advancing [44]. Whichever chemistry is used, the most difficult part would be choosing the catalytic domain, and coupling motion of the catalytic domain to the rest of the structure [45].

Only a small space of allosteric behavior is explored here, which is negative allostery. Even in modeling negative allosteric coupling in myosin, important behavior was left out. The most significant omission from this model is that ligand (actin) binding does not trigger the dissociation of the P_i analog P1. Including this reaction would require a more complex linkage, and is a logical next step in extending this model. Also, intramolecular 'self' binding, between parts of an enzyme, is not explored in this model. Exploring such design with linkages might be interesting, possibly in the context of trying to design cooperative binding or positive allostery. For example, kinesin, which has a neck-linker domain that reversibly binds to its ATPase domain, uses intramolecular 'self' binding of the neck-linker as a form of kinetic control [46].

The geometries I use are two-dimensional and simple compared to the complex three-dimensional geometries seen in proteins and ribonucleoproteins. It is possible that what the linkages represent are allosteric control centers - small dynamic geometries around which larger frameworks can be built that amplify the motion of the control center, as postulated for myosin [47, 48]. A major challenge in studying biomolecular machines is figuring out which structures are essential to the function they demonstrate, and which may be nonessential [49–51]. Synthetic systems allow a start from first principles, using select information gathered from nature. In the case of allostery this is information about the timing of reactions within cycles and the desired behavioral output. In order to use this information to engineer synthetic machines that function allosterically and autonomously, a clear design methodology is needed. The linkage model presented here is intended to be a contribution towards creating such a methodology.

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Note on article revision

This version of the article replaces the first version of the article, entitled 'Allosteric linkages that emulate a molecular motor enzyme'. This version is an updated presentation of the 'chemical cycle' material, which includes improved representations of the linkages, more in depth analysis of the simulation data and an extensive supplement. The first version includes some discussion on mechanical cycles, and a model of a dimer that walks along a track, which are not discussed in this version. I intend to revisit that 'mechanical' material in greater depth in a separate article some time in the future.

Supplemental

0.1 Displacement network with all connections drawn

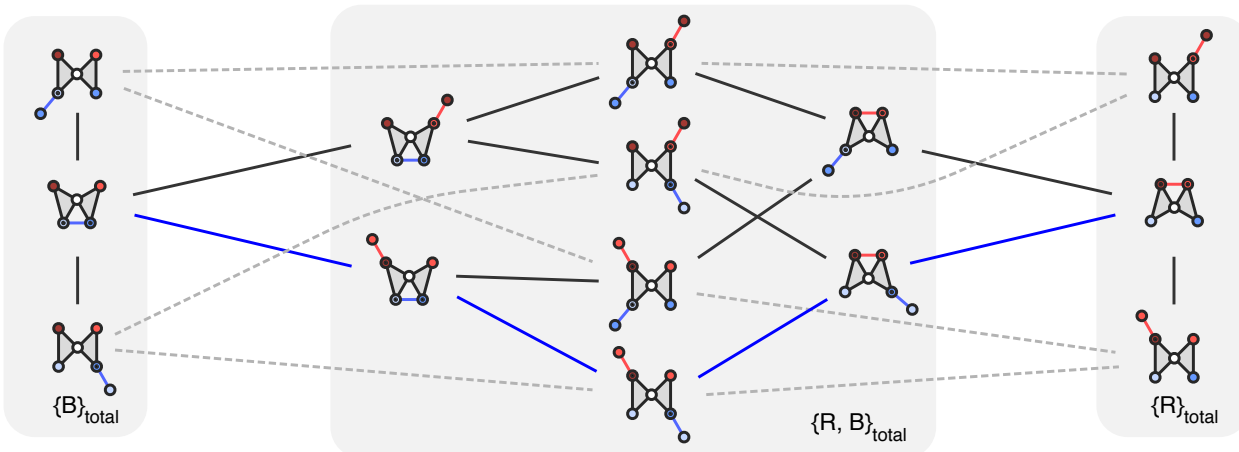
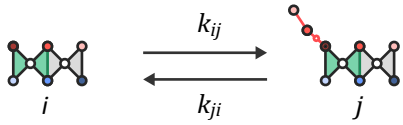


Fig. 12. Displacement network showing all possible transitions. This network shows the full set of bound states with single copies of B or R and the possible transitions between them. Each edge is a reversible reaction. The very bottom pathway in the network (blue) is the path shown in Fig. **??**. Intramolecular binding is assumed to be much faster than dissociation ($k_{\text{uni}} \gg k_{\text{off}}$'s), thus it is probable for R and B to be found divalently bound to M - the center states in $\{\text{B}\}_{\text{total}}$ and $\{\text{R}\}_{\text{total}}$. Hence, intermolecular transitions with these divalent states (drawn with solid lines) are highly favored, as they are the most likely transitions to take place. The binding transitions along the dotted lines take place between monovalently bound states, and only become more probable at extremely high concentrations of R or B, where the probability of binding (at a single node) from "solution" approaches the intramolecular binding rate, k_{uni}.

0.2 Converting node energies into off rates

Here, an expression is derived for calculating a node dissociation rate ($k_{\text{off-}node}$) in terms of its node energy (ε_{node}), and vice versa. This is done by satisfying local detailed balance for binding to and dissociation from a single node, as shown in the following figure:



State i is the unbound enzyme, and state j is the bound enzyme; k_{ij} is the rate for transitioning from i to j, and k_{ji} is the rate for transitioning from j to i. Although a specific reaction is shown in the figure, the setup of the derivation is general and can work for any node and molecule that binds that node.

If the equilibrium probability of being in state i is written as p_i, and for state j, written as p_j, then the equilibrium condition must satisfy:

$$k_{ij}p_i = k_{ji}p_j \tag{3}$$

The equilibrium probabilities are given by the Boltzmann factors for each state, divided by the partition function:

$$p_i = \frac{e^{-\beta G_i}}{Z} \tag{4}$$

where G_i is the free energy of the state. Using the above expression for p_i and p_j in equation 3, allows the transition rates to be expressed in terms of the state energies:

$$\frac{k_{ij}}{k_{ji}} = e^{\beta(G_j - G_i)} \tag{5}$$

The goal is to replace the above free energies with expressions relevant to states of the linkage. To do this, I closely follow the modeling done in Marzen et al. [52] for a "one-site MWC molecule", except I leave out the enzyme's "activated" state and its corresponding energy:

State	Energy	Boltzmann factor
	ε_l	$e^{-\beta\varepsilon_l}$
	$\varepsilon_l + \varepsilon_{node} - \mu$	$e^{-\beta(\varepsilon_l+\varepsilon_{node}-\mu)}$

Table 4

In Table 4, ε_l is the conformational energy of the enzyme (or receptor), and ε_{node} is the binding energy of the node. The full expression for μ, the chemical potential, which is described in Marzen et al. [52] as the "free energy cost of removing a ligand from dilute solution", is:

$$\mu = \mu_0 + k_B T \ln \frac{c}{c_0} \tag{6}$$

where μ_0 is an "unspecified reference chemical potential", and c_0 is an "unspecified reference concentration".

Equation 5 can be re-expressed in terms of the energies in Table 4 by letting $G_i = \varepsilon_l$ and $G_j = \varepsilon_l + \varepsilon_b - \mu$, and by using the full expression for μ in equation 6:

$$\frac{k_{ij}}{k_{ji}} = \frac{c}{c_0} e^{-\beta(\varepsilon_{node} - \mu_0)} \tag{7}$$

In the final step, k_{ij}, a binding rate, is expressed as the concentration (c) of the molecule binding, multiplied by a bimolecular rate constant (k_{bi}), so that $k_{ij} = ck_{\text{bi}}$; and k_{ij}, a dissociation rate, is renamed $k_{\text{off-}node}$. Making these two substitutions and solving for $k_{\text{off-}node}$, gives:

$$k_{\text{off-}node} = c_0 k_{\text{bi}}\, e^{-\beta \Delta\varepsilon_{node}} \tag{8}$$

where $\Delta\varepsilon_{node} = \mu_0 - \varepsilon_{node}$. Taking the log of both sides allows the node energy to be solved for in terms of the dissociation rate:

$$\Delta\varepsilon_{node} = -k_B T \ln\left(\frac{k_{\text{off-}node}}{c_0 k_{\text{bi}}}\right) \tag{9}$$

0.2.1 Condition for choosing rates

The main condition used for determining the rates was that the energies for the substrate, ligand and P2 satisfied the following inequality:

$$\varepsilon_{\text{substrate}} < \varepsilon_{\text{ligand}} < \varepsilon_{\text{P2}} \tag{10}$$

which means that substrate must bind tighter than ligand, which must bind tighter than P2. Each molecule's energy can be expressed as a summation of its node energies:

$$\underbrace{\varepsilon_{\text{a}} + \varepsilon_{\text{b}} + \varepsilon_{\text{c}}}_{\varepsilon_{\text{substrate}}} < \underbrace{\varepsilon_{\text{d}} + \varepsilon_{\text{e}} + \varepsilon_{\text{f}}}_{\varepsilon_{\text{ligand}}} < \underbrace{\varepsilon_{\text{b}} + \varepsilon_{\text{c}}}_{\varepsilon_{\text{P2}}} \tag{11}$$

0.3 Displacement of ligand by substrate

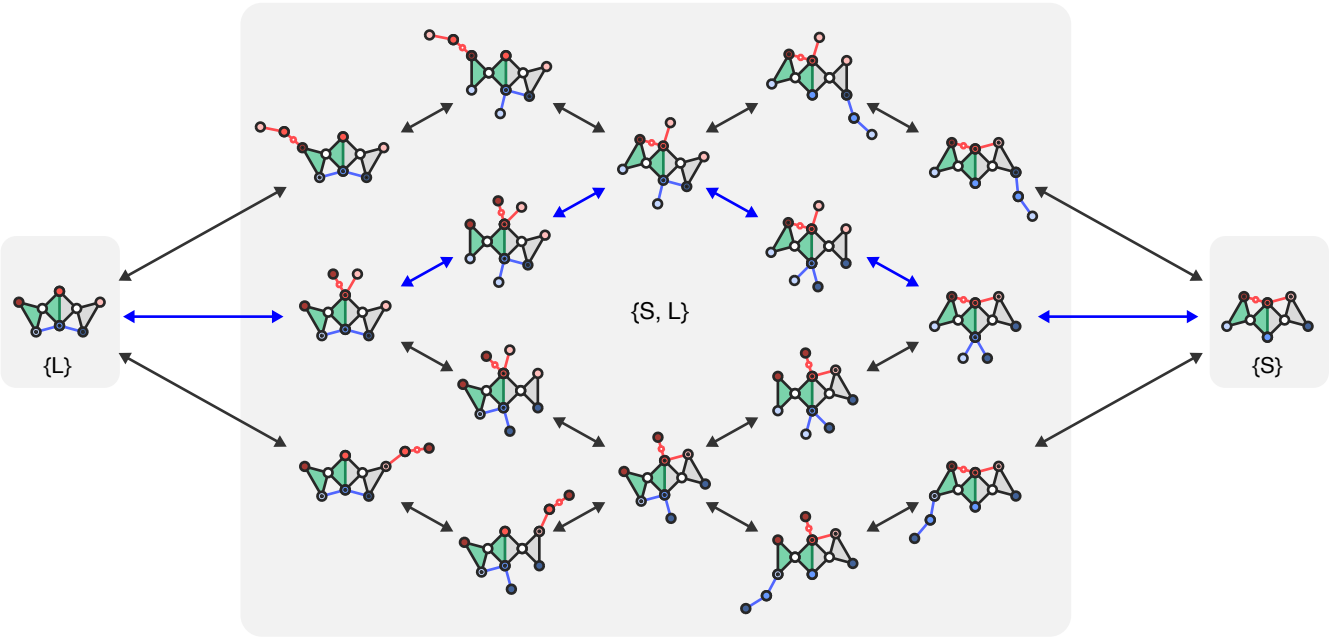


Fig. 13. Network representation of S allosterically displacing L. The blue colored pathway is the pathway used in Figs. 7 & 8 in the main text. Note that this is still a partial network that represents the most probable paths taken, given that intramolecular binding is much faster that intermolecular binding at low concentrations of S ($k_{\text{uni}} \gg k_{\text{S}}$), and always much faster than dissociation ($k_{\text{uni}} \gg k_{\text{off}}$'s). The complete network also accounts for the less probable transitions between states in which intermolecular binding takes place before intramolecular binding, and in which multiple intramolecular dissociations take place before intramolecular binding.

0.4 Target cycle of the two-unit system with all the transition rates

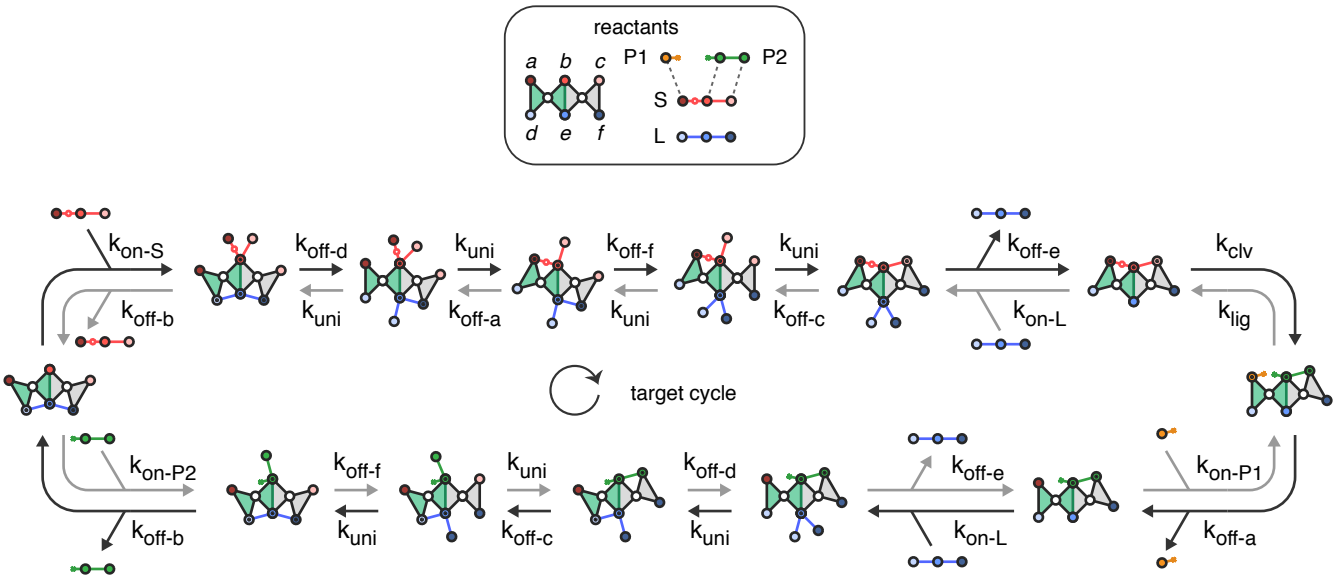


Fig. 14. Two-unit target cycle with rates.

0.5 Allosteric vs steric displacement

Fig. 15, a reaction coordinate plot, gives an alternative viewpoint on how the allosteric displacement pathway wins over the steric pathway. States along the two pathways are plotted using binding energies that are used for the stochastic simulations. Both pathways need to surmount the same bipartite activation barrier of P2 dissociation (nodes b and c) to achieve stable binding. The difference is that the allosteric pathway can save the highest energy barrier crossing (node b) for the end, after ligand has already bound metastably to the enzyme. This ordering makes it more probable for the first ligand that binds to remain bound and overcome the barrier. By contrast, multiple binding attempts by substrate are required to overcome the less favorable ordering of the P2 barrier that substrate experiences (node b, then node c). Hence, while both pathways rely on spurious thermal dissociations of P2 for forward progress, the allosteric pathway can more easily exploit the random timing of these dissociations from an allosteric binding site, rather than through direct competition.

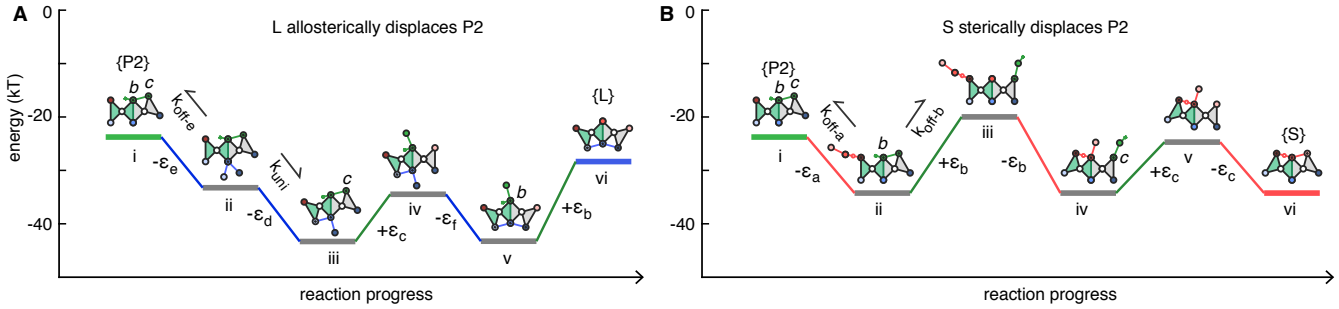


Fig. 15. Allosteric displacement vs steric displacement. In this plot the energy landscape traversed by the allosteric and steric displacement pathways are shown on a reaction coordinate, with energy given in kT units, and referenced to the empty state ({ø}) as zero kT. Both the allosteric and steric displacement reactions must overcome the same uphill activation barrier, which is the energy required to break the two bonds P2 makes with the enzyme ($+\epsilon_{\mathrm{P2}} = \epsilon_b + \epsilon_c$)), starting at the {P2} state (i). Along the allosteric pathway (going right from i), the ligand easily overcomes the barrier from the metastable basin it rapidly reaches, after binding divalently to the left side of the enzyme (allosteric displacement; i $\rightarrow$ iii). From this metastable basin, a single ligand can overcome the two-part barrier in either order, and over many attempts. The figure shows the weaker step being overcome first (iii $\rightarrow$ v), which is the most probable pathway. Conversely, the steric pathway (going left from i) is more ordered and reversible because the substrate and P2 compete directly for nodes and must alternate. Upon binding, the substrate is initially restricted to node a (steric pathway; i $\rightarrow$ ii), and consequently, the substrate must wait for P2 to dissociate from the more stable b node (ii $\rightarrow$ iii) in order to make a second bond with the enzyme (iii $\rightarrow$ iv). This makes it probable for any single substrate that binds to node a to dissociate, hence multiple binding attempts by substrate are needed for substrate to sterically displace P2.

0.6 Constructing the reaction networks

The reaction networks were constructed in these four steps:

1. Generate basis states.
2. Map exclusion rules between basis states.
3. Generate complete set of states.
4. Connect states to one another.

Each of these four steps are described in detail below:

1. **Generate basis states.** The basis states were created by enumerating all the ways the single reactants can bind to the enzyme. For the one-unit system there are nine basis states including the empty state (SI Fig. 16), and for the two-unit system there are seventeen basis states including the empty state (SI Fig. 17). The two-unit basis states excludes two geometrically possible states by invoking an ad hoc principle, named the *adjacency rule*, that only adjacent multivalent bonds can form (SI Fig. 18).

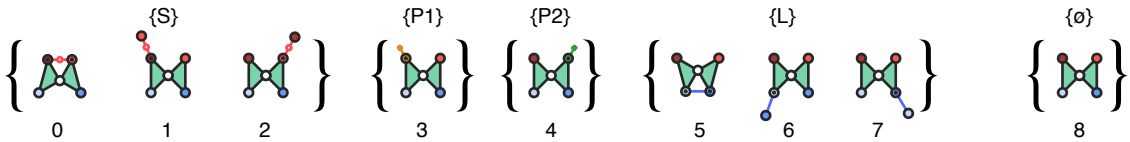


Fig. 16. One-unit bases states. The subset of eight basis states of the one-unit system, which includes the empty state ({ø}). In each of these states (save {ø}) only one molecule of S, P1, P2 or L is bound, and the subset of states enumerates all the different ways these four molecules can bind to the enzyme.

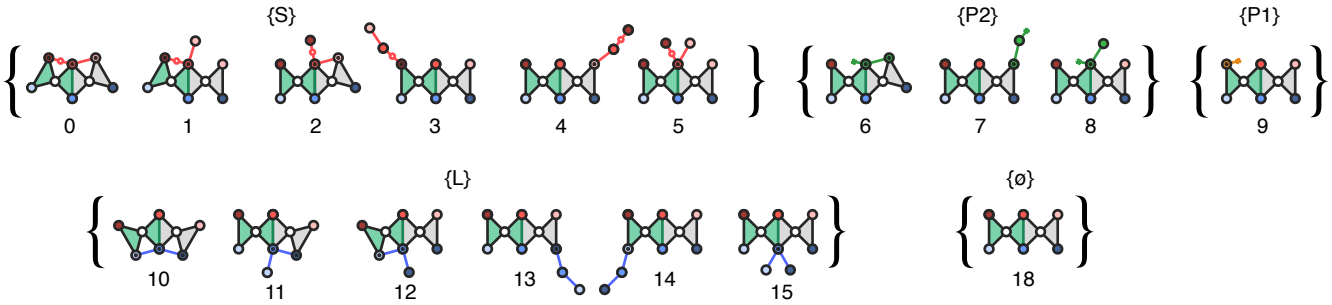


Fig. 17. Two-unit basis states. Subset of seventeen states that are used to generate and name the complete set of 449 states. In each of these states only one molecule of S, P1, P2 or L is bound, and the subset of states enumerates all the different ways these four molecules can bind to the enzyme, barring the two states eliminated by the adjacency rule.

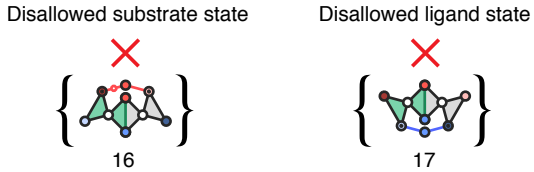


Fig. 18. Adjacency rule. Only adjacent bonds are allowed to form or dissociate between two interacting linkages. Left, disallowed substrate state in which the two outer nodes are bound, and the central node is dissociated. Right, disallowed ligand state in which the two outer nodes are bound, and the central node is dissociated.

2. **Map exclusion rules between basis states.** The exclusion rules for each system are mapped out as a binary matrix that matches the three sets of substrate and product basis states against the set of ligand binding basis states. For each matchup, the two states can either coexist together on the enzyme, and thus are an allowed two-molecule-bound state, or they cannot coexist together on the enzyme, and thus are an excluded two-molecule-bound state (symbolized by). What should be noticed is that excluded states only result from matching one multivalent state to another multivalent state. Thus, the one-unit system has only one excluded state ({0, 5}), and the two-unit system has nine excluded states: seven for S and L ({1, 12}, {0, 12}, {1, 10}, {0, 10}, {2, 10}, {0, 11}, and {2, 11}); and two for P2 and L ({6, 10} and {6, 11}).

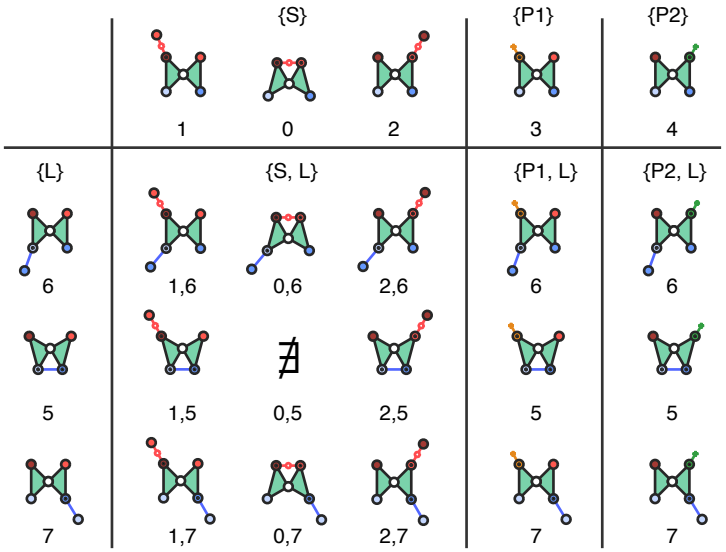


Fig. 19. One-unit rules matrix This binary matrix graphically displays the geometric restrictions that exist between the basis states in the one-unit system, and which each represent an instance of negative allosteric coupling. The single pairing of of basis states that cannot coexist is $\{5\}$ and $\{0\}$, or $\{0, 5\}$, which is labeled with $\nexists$, for "does not exist".

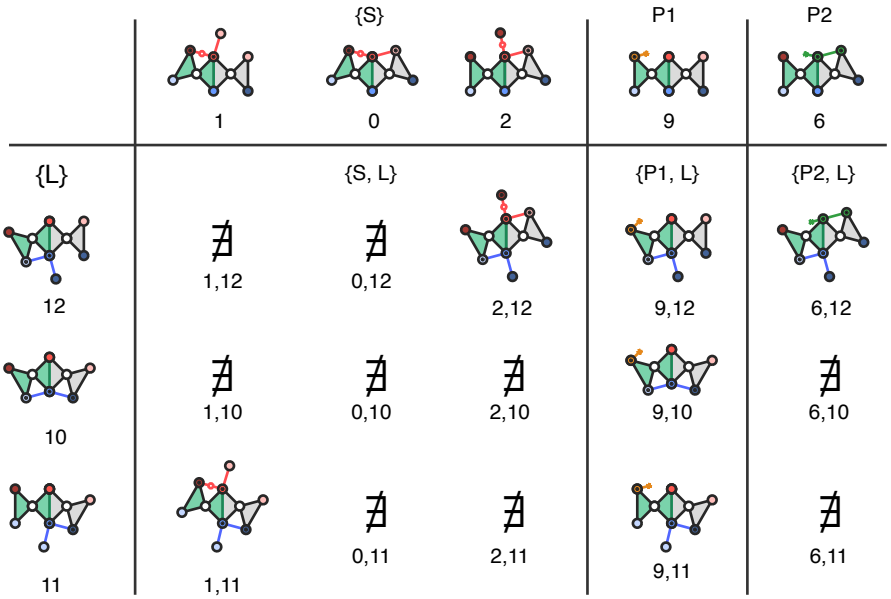


Fig. 20. Two-unit rules matrix. This binary matrix graphically displays the geometric restrictions that exist between the basis states, and which each represent an instance of negative allosteric coupling. Basis states that cannot coexist, and thus generate a new state, are represented with $\nexists$, for "does not exist". Here, because of the two degrees of freedom, there are nine conflicts, by contrast to the one conflict in the one-unit system. Note that P1 and the ligand-bound-states ($\{L\}$) do have any conflicts, because P1 is bound monovalently to the enzyme.

3. **Generate complete set of states.** [Notations used: B^n, where $n = 0$ to 6, denotes sets of states with n number of molecules bound to the enzyme. For example, B^0 is the empty state, and B^1 is the set

of one-molecule-bound basis states (see. Figs. 16 & 17). $\mathbf{B}^n$, for $n > 1$, is the matrix form of each set of bound states, and $\mathbf{B}^n_m$, refers to the row of the matrix, where the subscript m denotes a state written as a set of basis states (e.g. if $m = 0, 13$, this means state $\{0, 13\}$). In the matrix, '0' means the states cannot coexist, and '1' means that can coexist. Hence, '0' is equivalent to the $\nexists$ symbol used in Figs. 19 & 20.]

Sets of higher order bound states were successively generated by multiplying (as a binary matrix) the set of states with one molecule less, with the set of basis states B^1 (e.g. $B^4 = B^3 \times B^1$). The process starts with the generation of B^2, where $B^2 = B^1 \times B^1$:

$\mathbf{B^2} =$

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
1	0	0	0	0	1	0	0	1	0	0	0	1	0	1	1	1
2	0	0	0	1	0	0	0	0	0	1	0	0	1	1	1	1
3	0	0	1	0	1	1	1	1	1	0	1	1	1	1	1	1
4	0	1	0	1	0	1	0	0	1	1	1	1	1	1	1	1
5	0	0	0	1	1	0	0	1	0	1	1	1	1	1	1	1
6	0	0	0	1	0	0	0	0	0	1	0	0	1	1	1	1
7	0	1	0	1	0	1	0	0	1	1	1	1	1	1	1	1
8	0	0	0	1	1	0	0	1	0	1	1	1	1	1	1	1
9	0	0	1	0	1	1	1	1	1	0	1	1	1	1	1	1
10	0	0	0	1	1	1	0	1	1	1	0	0	0	0	0	0
11	0	1	0	1	1	1	0	1	1	1	0	0	0	0	1	0
12	0	0	1	1	1	1	1	1	1	1	0	0	0	1	0	0
13	1	1	1	1	1	1	1	1	1	1	0	0	1	0	1	1
14	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0	1
15	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	0

The resulting $\mathbf{B}^2$ matrix has two uses: 1) it generates the two-molecule-bound states, which are indicated wherever a '1' appears in the matrix; and 2) it generates a set of row vectors $\mathbf{B}^2_m$ to compliment each basis state m in B^1, which are in turn used as multipliers to generate the higher order states. For example, the '1' in row 0, column 13, represents state $\{0, 13\}$ in B^2. To generate B^3 ($B^3 = B^2 \times B^1$), each state in B^2 is converted into a row vector for $\mathbf{B}^3$, using the set of basis vectors $\mathbf{B}^2_m$. This is done by performing an element wise multiplication of the basis vectors that comprise each state in B^2. Hence, state $\{0, 13\}$ is converted into row vector $\mathbf{B}^3_{0,13}$ in $\mathbf{B}^3$ by multiplying basis vectors $\mathbf{B}^2_0$ and $\mathbf{B}^2_{13}$ together element-wise, which is expressed as the Hadamard product, where '$\circ$' means element-wise multiplication:

$$\begin{aligned}\mathbf{B}^3_{0,13} = \mathbf{B}^2_0 \circ \mathbf{B}^2_{13} = &[\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 1\ 1\ 1\ ] \circ \\ &[\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 0\ 0\ 1\ 0\ 1\ 1\ ] = \\ &[\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 1\ 1\ ]\end{aligned}$$

Thus, for every '1' in $\mathbf{B}^2$, the Hadamard product is used to construct the rows of $\mathbf{B}^3$:

$\mathbf{B^3} =$

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0, 13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
0, 14	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
0, 15	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	0
1, 4	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1
1, 7	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1
1, 11	0	0	0	0	1	0	0	1	0	0	0	0	0	0	1	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
16, 17	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	1

To generate $\mathbf{B}^4$ the process is repeated. For example, the row vector $\mathbf{B}^4_{0,13,14}$ is generated by the product of $\mathbf{B}^3_{0,13}$ and basis vector $\mathbf{B}^2_{14}$:

$$\begin{aligned}\mathbf{B}^4_{0,13,14} = \mathbf{B}^3_{0,13} \circ \mathbf{B}^1_{14} = &[\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 1\ 1\ ] \circ \\ &[\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 0\ 1\ 0\ 1\ 0\ 1\ ] = \\ &[\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 1\ ]\end{aligned}$$

If $\mathcal{B}_{1unit}$ and $\mathcal{B}_{2unit}$ are used to symbolize the full set of states in the one and two-unit systems, respectively, then $\mathcal{B}_{1unit} = \{B^0, B^1, B^2, B^3, B^4\}$ and $\mathcal{B}_{2unit} = \{B^0, B^1, B^2, B^3, B^4, B^5, B^6\}$, where B^0 is the empty state, and the number of higher order sets reflects the number of nodes in each system: four in the one-unit system; and six in the two-unit system. The number of states in each set is given directly below in Table (). A list of states for the one-unit system ($\mathcal{B}_{1unit}$) are given in section (), and for the two-unit system ($\mathcal{B}_{2unit}$) in section 0.3.

Set	one-unit	two-unit
B^0	1	1
B^1	9	17
B^2	19	74
B^3	17	150
B^4	4	142
B^5	-	58
B^6	-	8
$\mathcal{B}$ (total)	49	449

Table 5: **Number of states in each set.**

4. **Connect states to one another.** The states were connected together in two stages: (i) a unique set was constructed in which each member was a pair of states that could reversibly transition to one another; and (ii) each direction of the pair was again classified by reaction type and assigned with the appropriate rate. The process has some redundancy because pairs were classified by reaction type at both stages. In principle this could have been done once, but this is the way I chose to do it. First I describe stage 1 in more detail, and then stage 1:

i. Constructing a unique set of transition pairs: This process was done in three parts: (a) finding pairs that define bimolecular binding/dissociation; (b) finding pairs that define intramolecular binding/dissociation; and (c) finding pairs that define catalysis/ligation. These three categories are described individually below:

a. Finding bimolecular binding/dissociation pairs: These pairs were found using a matrix called the binding matrix ($\mathbf{b}$), which describes whether two basis states in the B^1 set can combine to form a new state by a binding reaction, with the addition of a row for the empty state ($\{18\}$ or B^0):

$\mathbf{b} =$

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
1	0	0	0	0	1	0	0	1	0	0	0	0	0	1	1	1
2	0	0	0	1	0	0	0	0	0	1	0	0	0	1	1	1
3	0	0	0	0	1	1	0	1	1	0	0	0	0	1	1	1
4	0	0	0	1	0	1	0	0	1	1	0	0	0	1	1	1
5	0	0	0	1	1	0	0	1	0	1	0	0	0	1	1	1
6	0	0	0	1	0	0	0	0	0	1	0	0	0	1	1	1
7	0	0	0	1	0	1	0	0	1	1	0	0	0	1	1	1
8	0	0	0	1	1	0	0	1	0	1	0	0	0	1	1	1
9	0	0	0	0	1	1	0	1	1	0	0	0	0	1	1	1
10	0	0	0	1	1	1	0	1	1	1	0	0	0	0	0	0
11	0	0	0	1	1	1	0	1	1	1	0	0	0	0	1	0
12	0	0	0	1	1	1	0	1	1	1	0	0	0	1	0	0
13	0	0	0	1	1	1	0	1	1	1	0	0	0	0	1	1
14	0	0	0	1	1	1	0	1	1	1	0	0	0	1	0	1
15	0	0	0	1	1	1	0	1	1	1	0	0	0	1	1	0
18	0	0	0	1	1	1	0	1	1	1	0	0	0	1	1	1

The matrix $\mathbf{b}$ maps out a subset of the pairs in $\mathbf{B^2}$, with entries that reflect only allowed single-node interactions. An entry of a '1' at a given column position means that the basis state at that column position can combine with the basis state for that row to form a new state that contains the row basis state and the column basis state, where the column state is the new molecule that binds at a single node. Hence, each row can be thought of as a basis vector for binding. And thus, for every state in the system, a combined binding vector could be calculated using the Hadamard product in the exact same way it was done to find successive higher order states. For example, to find the binding vector $\mathbf{b_{1,13}}$ for state {1, 13}, the binding vectors for {1} and {13} are multiplied together:

$$\begin{aligned}\mathbf{b}_{1,13} = \mathbf{b}_1 \circ \mathbf{b}_{13} = &[\ 0\ 0\ 0\ 0\ 1\ 0\ 0\ 1\ 0\ 0\ 0\ 0\ 0\ 1\ 1\ 1\ ] \circ \\ &[\ 0\ 0\ 0\ 1\ 1\ 1\ 0\ 1\ 1\ 1\ 0\ 0\ 0\ 0\ 1\ 1\ ] = \\ &[\ 0\ 0\ 0\ 0\ 1\ 0\ 0\ 1\ 0\ 0\ 0\ 0\ 0\ 0\ 1\ 1\ ]\end{aligned}$$

As there is a '1' at positions $\{4\}, \{6\}, \{14\}$, and $\{15\}$, state $\{1, 13\}$ can make four different binding transitions to new states containing these basis states, and in reverse, dissociations take place to transition to state $\{1, 13\}$:

$$\begin{aligned}\{1,13\} &\rightleftharpoons \{1,4,13\} \\ \{1,13\} &\rightleftharpoons \{1,6,13\} \\ \{1,13\} &\rightleftharpoons \{1,13,14\} \\ \{1,13\} &\rightleftharpoons \{1,13,15\}\end{aligned} \tag{12}$$

Hence, for every state in the system, the process is repeated to find all the possible bimolecular binding/dissociation transitions.

b. Finding intramolecular binding/dissociation pairs: These pairs were found using a matrix, the isomerization matrix ($\mathbf{i}$), that describes which states can transition to another by an intramolecular binding/dissociation reaction. For example, when the ligand or substrate are bound at two nodes, and make a third association with the enzyme, and vice versa for dissociation:

$$
\mathbf{i} = \begin{array}{c|cccccccccccccccc}
 & 0 & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & 11 & 12 & 13 & 14 & 15 \\
\hline
0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
2 & 1 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
3 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
4 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
5 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
6 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
7 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
8 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
9 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
10 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 \\
11 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 1 \\
12 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 1 \\
13 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
14 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
15 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0
\end{array}
$$

Like $\mathbf{b}$, $\mathbf{i}$ is a subset of the pairs defined in $\mathbf{B}^2$. The possible isomerizations indicated by $\mathbf{i}$ cannot conflict with any other molecule that is bound to the enzyme, where the conflict can be either steric or allosteric. For example, the state {1, 14} does not have any conflicts, but {1, 12} does have an allosteric conflict, even though {14} can transition to {12} when it is on the enzyme alone. Hence, to account for conflicts, $\mathbf{i}$ is used with $\mathbf{B}^2$ in the following way. To test for isomerizations, each basis state in a state is tested individually by taking the Hadamard product of its $\mathbf{i}$ vector and the $\mathbf{B}^2$ basis vectors for all the other basis states in the state. For example, to test state {3, 12, 13} for isomerizations, {3}, {12}, and {13} are tested separately. Testing {3} first is done by multiplying $\mathbf{i}_3$ by $\mathbf{B}^2_{12}$ and $\mathbf{B}^2_{13}$, which shows that {3} cannot isomerize when present with {12}, and {13}; or substrate on node a cannot bind any other node when one ligand is bound divalently at d and e, and another is bound at f:

$$
\begin{aligned}
\mathbf{i}_3 \circ \mathbf{B}^2_{12} \circ \mathbf{B}^2_{13} = {} & [\ 0\ 1\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ ] \circ \\
& [\ 0\ 0\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 0\ 0\ 0\ 1\ 0\ 0\ ] \circ \\
& [\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 0\ 0\ 1\ 0\ 1\ 1\ ] = \\
& [\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ ]
\end{aligned}
$$

Testing {12}, reveals one possible isomerization to state {3, 13, 14}:

$$
\begin{aligned}
\mathbf{i}_{12} \circ \mathbf{B}^2_{3} \circ \mathbf{B}^2_{13} = {} & [\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 1\ 0\ 0\ 0\ 1\ 1\ ] \circ \\
& [\ 0\ 0\ 1\ 0\ 1\ 1\ 1\ 1\ 1\ 0\ 1\ 1\ 1\ 1\ 1\ 1\ ] \circ \\
& [\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 1\ 0\ 0\ 1\ 0\ 1\ 1\ ] = \\
& [\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 1\ 1\ ]
\end{aligned}
$$

where in this isomerization the divalently bound ligand is dissociating from node d or e. Testing {13} results in no other isomerizations. Hence the final result is that {3, 12, 13} isomerizes to {3, 13, 14} and {3, 13, 15}, where because basis states are ordered numerically, {14} and {15} are written after {13} in the new states, though they are isomerization of {12}:

$$
\begin{aligned}
\{3, 12, 13\} &\rightleftharpoons \{3, 13, 14\} \\
\{3, 12, 13\} &\rightleftharpoons \{3, 13, 15\}
\end{aligned}
\tag{13}
$$

To describe the transitions in terms of the molecules: in the forward direction, the divalently bound ligand dissociates from node d or e, and in the reverse direction, the same ligand rebinds binds at node d or e.

c. Finding cleavage/ligation pairs: These pairs were found by looking for all states that contain {0} the fully bound substrate, and converting {0} to {6} and {9}, where {6} is P1 bound at node a, and {9} is P2 bound divalently. Any state that contains {0} automatically accounts for the reaction in both directions and rules out any geometric conflicts, because the substrate can only be fully bound when there are no geometric conflicts. Thus any state generated by converting {0} to {6} and {9} is a ligation ready state without geometric conflicts, which specifically means they do not contain basis states {11} or {12}.

ii. Assigning rates to each direction of a reaction pair: Rates were assigned using a series of logical statements that checked to see what kind of forward and reverse reactions a pair of states described, and then assigned rates accordingly: dissociations were assigned rates based on the node from which the dissociation took place, bimolecular binding reactions were assigned the bimolecular binding rate constant multiplied by a factor that reflected the concentration of the molecule binding, intramolecular binding reactions were all assigned the same unimolecular rate (k_{uni}); and cleavage and ligation reactions were assigned the same rate (k_{cat}) (see tables 5, 6, and 7, which are repeated from the main text.)

Table 6: Categories of reaction rates

Parameter	Value
Bimolecular rate constant, k_{bi}	$9 \times 10^6\,\text{M}^{-1}\text{s}^{-1}$
Concentration, c_m (m = S, P1, P2, L)	varies with m; units of M
Intermolecular binding rates, k_m	$k_{\text{bi}} \times c_m\ \text{s}^{-1}$
Intramolecular binding rate, k_{uni}	$1 \times 10^6\,\text{s}^{-1}$
Dissociation rates, $k_{\text{off-}node}$	varies with *node*; units of s^{-1}
Catalysis, k_{cat}	$100\,\text{s}^{-1}$

Table 7: one-unit dissociation rates

Rate	Reactants	Value
$k_{\text{off-a}}$	S/P1	$250\,\text{s}^{-1}$
$k_{\text{off-b}}$	S/P2	$3\,\text{s}^{-1}$
$k_{\text{off-d}}$	L	$200\,\text{s}^{-1}$
$k_{\text{off-e}}$	L	$680\,\text{s}^{-1}$

Table 8: two-unit dissociation rates

Rate	Reactants	Value
$k_{\text{off-a}}$	S/P1	$250\,\text{s}^{-1}$
$k_{\text{off-b}}$	S/P2	$3\,\text{s}^{-1}$
$k_{\text{off-c}}$	S/P2	$680\,\text{s}^{-1}$
$k_{\text{off-d}}$	L	$680\,\text{s}^{-1}$
$k_{\text{off-e}}$	L	$200\,\text{s}^{-1}$
$k_{\text{off-f}}$	L	$680\,\text{s}^{-1}$

0.7 Stochastic formulation of the rates

The rates expressed in table 5 in the SI (table 1 in main text) were input as stochastic rates in the simulations (table 8 in SI). To express the rates stochastically, a scaling factor was used, which is a reaction volume multiplied by Avogadro's number ($N_A \times v$). By dividing the bimolecular rate constant (k_{bi}) by

this scaling factor, k_{bi}, which has units of $\text{M}^{-1}\text{s}^{-1}$, and which retains some relevance to reaction rates for real biomolecules, was converted into a stochastic version, k^*_{bi}, with units of s^{-1}. Likewise, concentrations, c_m's, which have units of M, were multiplied by the scaling factor to convert them into their stochastic versions, c^*_m's, which have units of "number of molecules" (No.).

Table 9: Stochastic conversions of rates

Parameter	Value
Volume, v	$1 \times 10^{-12}\,\text{m}^3$
Scaling factor, $N_A \times v$	$6.022 \times 10^{11}\,\text{M}^{-1}$
Stoch. bimol. rate constant, $k^*_{\text{bi}} = k_{\text{bi}}/(N_A \times v)$	$9/6.022 \times 10^{-5}\,\text{s}^{-1}$
Stoch. "concentration", $c^*_m = c_m \times (N_A \times v)$	varies with m; units of No.
Intermolecular binding rates, k_m	$k^*_{\text{bi}} \times c^*_m$ (or $k_{\text{bi}} \times c_m$)

0.8 Maximum turnover rate in the one-unit system

The maximum turnover rate (V_{max}) without ligand is approximately the rate at which it takes the system goes to complete catalysis, P1 dissociation and P2 dissociation (ignoring the substrate binding step which is very fast relative to the other steps at very high concentrations of S):

$$V_{\text{max}} \approx (1/k_{\text{off-a}} + 1/k_{\text{cat}} + 1/k_{\text{off-b}})^{-1} = 2.8\ \text{s}^{-1} \tag{14}$$

Here, P2 dissociation is rate limiting, because it is the slowest step ($k_{\text{off-b}} = 3\ \text{s}^{-1}$).

0.9 Analyzing trajectories

In this section I use a kinetic cube to describe the way Python code was written in order to look for the various good and bad pathways that could be taken. The kinetic cube has ten vertices, eight that exist on corners of the cube and two that exist on diagonals. Each of these vertices represents a significant bound state of the enzyme. Pathways drawn on the cube are used to represent changes to the bound state during a simulation.

A complete pathway is defined as including the loading of substrate, catalysis, and the release of P2. To define all the possibilities, pathways were initially broken up into beginnings and endings, which could either be "good" or "bad", where "good" means it *is* part of a productive cycle, and "bad" means that it is *not* part of a productive cycle. To be a complete productive cycle, the pathway has to begin, and end "good", though there is only one way to begin "good". Beginnings define the loading of substrate (if the path did not start at {S}) and the catalysis event, ending with at least P1 and P2 bound to the enzyme, and they start at either {L}, {S}, {P2} or {ø}. Endings define the release of P2 from the enzyme, starting from {P1, P2} or {P2}.

By using a series of logical statements that allowed the beginnings and endings pictured in Fig. 21 to be combined and mutually excluded from one another, all the possible pathways could be enumerated, as visually represented in Fig. 22. Mutual exclusivity here means that the sum of the pathways counted equals the total number of P2's released during a trajectory. Not every pathway was explicitly searched for. For example, productive cycles 1, 2, and 3 are all possible productive cycles based on the exclusion clauses and the definition of productivity, but they were not differentiated by the Python code that was used.

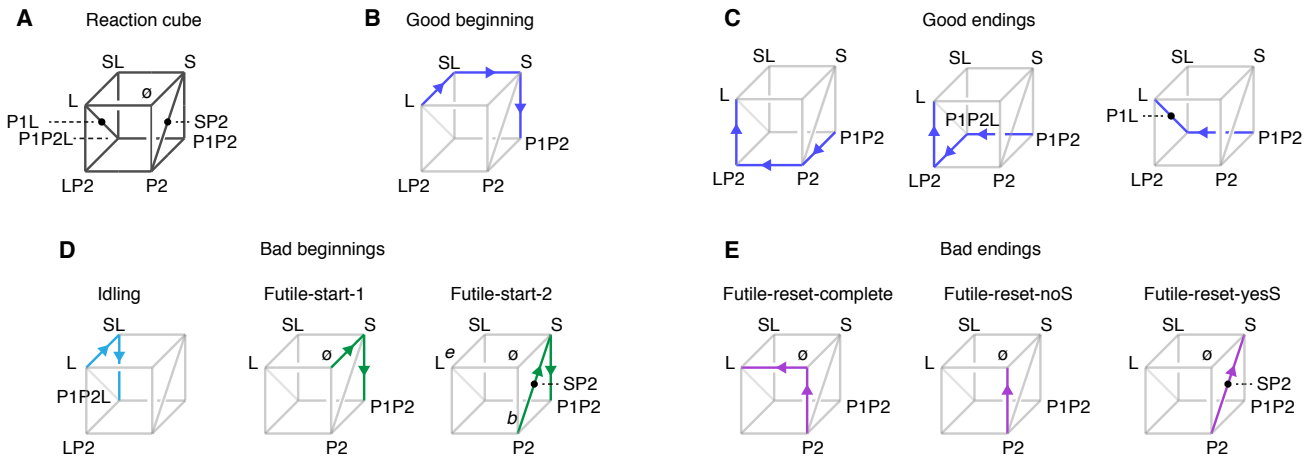


Fig. 21. Kinetic cube and partial trajectory pathways. A, Kinetic cube. This cube is used to represent possible simulation trajectories. There are ten vertices on the cube - eight on the cube corners and two on the diagonals - which represent the main binding states of the enzyme in combination with S, P1, P2 and L, where the binding state is written without commas or brackets for brevity. **B,** Good beginning. This is the beginning four state sequence of a productive pathway, during which substrate allosterically displaces ligand from the enzyme. **C,** Good endings. These are the three possible ways a productive pathway can end, where in each, ligand binds before P2 dissociates. **D,** Bad beginnings. These are the three bad beginnings, in which substrate is loaded and catalysis takes place, but not in the desired order. In Idling, ligand remains bound during catalysis, and in the futile-starts, substrate is loaded but without ligand being present, thus without the allosteric displacement of substrate by ligand. **E,** Bad endings. These are the three bad-endings, in which P2 dissociates from the enzyme, but without the presence of ligand, thus without the allosteric displacement of P2 by ligand.

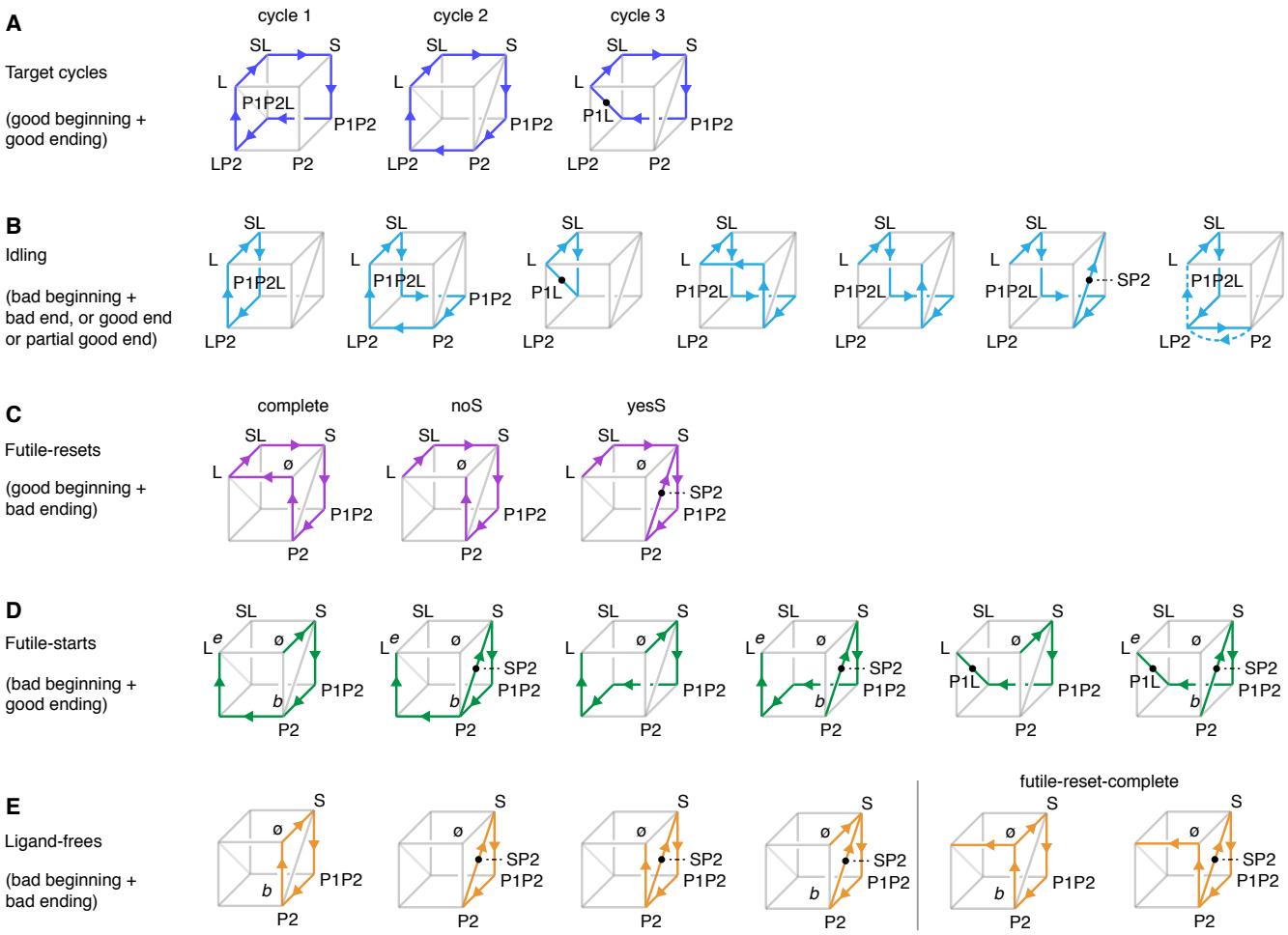


Fig. 22. Mutually exclusive pathways on the kinetic cube. Each pathway accounts for one loading of substrate, a catalysis event, and subsequent dissociation of P2. **A,** Target cycles. The three possible target cycles all show the displacement of ligand by substrate, followed by the displacement of P2 by ligand. **B,** Idling. The seven possible idling pathways, all of which start with the ligand remaining bound during catalysis. In the last pathway, the dotted line segments are the last two steps to take place in the sequence. This is the idling* pathway seen in Fig. 11A. **C,** Futile-resets. Futile resets start off like a productive pathway - with the displacement of ligand by substrate - but end "off-path" by going through the empty state, or by the steric displacement of P2 by substrate. **D,** Futile-starts. Futile starts begin "bad", but end "good", meaning they end with the displacement of P2 by ligand sequence. **E,** Ligand-frees. These are all the pathways that don't include ligand.

0.10 States of the one-unit system

{8}, {0}, {1}, {2}, {3}, {4}, {5}, {6}, {7}, {0, 6}, {0, 6, 7}, {0, 7}, {1, 2}, {1, 2, 5}, {1, 2, 6}, {1, 2, 6, 7}, {1, 2, 7}, {1, 4}, {1, 4, 5}, {1, 4, 6}, {1, 4, 6, 7}, {1, 4, 7}, {1, 5}, {1, 6}, {1, 6, 7}, {1, 7}, {2, 3}, {2, 3, 5}, {2, 3, 6}, {2, 3, 6, 7}, {2, 3, 7}, {2, 5}, {2, 6}, {2, 6, 7}, {2, 7}, {3, 4}, {3, 4, 5}, {3, 4, 6}, {3, 4, 6, 7}, {3, 4, 7}, {3, 5}, {3, 6}, {3, 6, 7}, {3, 7}, {4, 5}, {4, 6}, {4, 6, 7}, {4, 7}, {6, 7}

0.11 Transitions out of each state in the one-unit system

{8} → {1}, {2}, {3}, {4}, {6}, {7}
{0} → {1}, {2}, {0, 6}, {0, 7}, {3, 4}
{1} → {0}, {8}, {1, 2}, {1, 4}, {1, 6}, {1, 7}
{2} → {0}, {8}, {1, 2}, {2, 3}, {2, 6}, {2, 7}
{3} → {8}, {2, 3}, {3, 4}, {3, 6}, {3, 7}
{4} → {8}, {1, 4}, {3, 4}, {4, 6}, {4, 7}
{5} → {6}, {7}, {1, 5}, {2, 5}, {3, 5}, {4, 5}
{6} → {5}, {8}, {1, 6}, {2, 6}, {3, 6}, {4, 6}, {6, 7}

{7} → {5}, {8}, {1, 7}, {2, 7}, {3, 7}, {4, 7}, {6, 7}
{0, 6} → {1, 6}, {2, 6}, {0}, {0, 6, 7}, {3, 4, 6}
{0, 6, 7} → {1, 6, 7}, {2, 6, 7}, {0, 7}, {0, 6}, {3, 4, 6, 7}
{0, 7} → {1, 7}, {2, 7}, {0}, {0, 6, 7}, {3, 4, 7}
{1, 2} → {2}, {1}, {1, 2, 6}, {1, 2, 7}
{1, 2, 5} → {2, 5}, {1, 5}, {1, 2, 6}, {1, 2, 7}
{1, 2, 6} → {2, 6}, {1, 6}, {1, 2, 5}, {1, 2}, {1, 2, 6, 7}
{1, 2, 6, 7} → {2, 6, 7}, {1, 6, 7}, {1, 2, 7}, {1, 2, 6}
{1, 2, 7} → {2, 7}, {1, 7}, {1, 2, 5}, {1, 2}, {1, 2, 6, 7}
{1, 4} → {4}, {1}, {1, 4, 6}, {1, 4, 7}
{1, 4, 5} → {4, 5}, {1, 5}, {1, 4, 6}, {1, 4, 7}
{1, 4, 6} → {4, 6}, {1, 6}, {1, 4, 5}, {1, 4}, {1, 4, 6, 7}
{1, 4, 6, 7} → {4, 6, 7}, {1, 6, 7}, {1, 4, 7}, {1, 4, 6}
{1, 4, 7} → {4, 7}, {1, 7}, {1, 4, 5}, {1, 4}, {1, 4, 6, 7}
{1, 5} → {5}, {1, 6}, {1, 7}, {1, 2, 5}, {1, 4, 5}
{1, 6} → {0, 6}, {6}, {1, 5}, {1}, {1, 2, 6}, {1, 4, 6}, {1, 6, 7}
{1, 6, 7} → {0, 6, 7}, {6, 7}, {1, 7}, {1, 6}, {1, 2, 6, 7}, {1, 4, 6, 7}
{1, 7} → {0, 7}, {7}, {1, 5}, {1}, {1, 2, 7}, {1, 4, 7}, {1, 6, 7}
{2, 3} → {3}, {2}, {2, 3, 6}, {2, 3, 7}
{2, 3, 5} → {3, 5}, {2, 5}, {2, 3, 6}, {2, 3, 7}
{2, 3, 6} → {3, 6}, {2, 6}, {2, 3, 5}, {2, 3}, {2, 3, 6, 7}
{2, 3, 6, 7} → {3, 6, 7}, {2, 6, 7}, {2, 3, 7}, {2, 3, 6}
{2, 3, 7} → {3, 7}, {2, 7}, {2, 3, 5}, {2, 3}, {2, 3, 6, 7}
{2, 5} → {5}, {2, 6}, {2, 7}, {1, 2, 5}, {2, 3, 5}
{2, 6} → {0, 6}, {6}, {2, 5}, {2}, {1, 2, 6}, {2, 3, 6}, {2, 6, 7}
{2, 6, 7} → {0, 6, 7}, {6, 7}, {2, 7}, {2, 6}, {1, 2, 6, 7}, {2, 3, 6, 7}
{2, 7} → {0, 7}, {7}, {2, 5}, {2}, {1, 2, 7}, {2, 3, 7}, {2, 6, 7}
{3, 4} → {4}, {3}, {3, 4, 6}, {3, 4, 7}, {0}
{3, 4, 5} → {4, 5}, {3, 5}, {3, 4, 6}, {3, 4, 7}
{3, 4, 6} → {4, 6}, {3, 6}, {3, 4, 5}, {3, 4}, {3, 4, 6, 7}, {0, 6}
{3, 4, 6, 7} → {4, 6, 7}, {3, 6, 7}, {3, 4, 7}, {3, 4, 6}, {0, 6, 7}
{3, 4, 7} → {4, 7}, {3, 7}, {3, 4, 5}, {3, 4}, {3, 4, 6, 7}, {0, 7}
{3, 5} → {5}, {3, 6}, {3, 7}, {2, 3, 5}, {3, 4, 5}
{3, 6} → {6}, {3, 5}, {3}, {2, 3, 6}, {3, 4, 6}, {3, 6, 7}
{3, 6, 7} → {6, 7}, {3, 7}, {3, 6}, {2, 3, 6, 7}, {3, 4, 6, 7}
{3, 7} → {7}, {3, 5}, {3}, {2, 3, 7}, {3, 4, 7}, {3, 6, 7}
{4, 5} → {5}, {4, 6}, {4, 7}, {1, 4, 5}, {3, 4, 5}
{4, 6} → {6}, {4, 5}, {4}, {1, 4, 6}, {3, 4, 6}, {4, 6, 7}
{4, 6, 7} → {6, 7}, {4, 7}, {4, 6}, {1, 4, 6, 7}, {3, 4, 6, 7}
{4, 7} → {7}, {4, 5}, {4}, {1, 4, 7}, {3, 4, 7}, {4, 6, 7}
{6, 7} → {7}, {6}, {1, 6, 7}, {2, 6, 7}, {3, 6, 7}, {4, 6, 7}

0.12 States of the two-unit system

{18}, {0}, {1}, {2}, {3}, {4}, {5}, {6}, {7}, {8}, {9}, {10}, {11}, {12}, {13}, {14}, {15}, {0, 13}, {0, 13, 14}, {0, 13, 14, 15}, {0, 13, 15}, {0, 14}, {0, 14, 15}, {0, 15}, {1, 4}, {1, 4, 11}, {1, 4, 11, 14}, {1, 4, 13}, {1, 4, 13, 14}, {1, 4, 13, 14, 15}, {1, 4, 13, 15}, {1, 4, 14}, {1, 4, 14, 15}, {1, 4, 15}, {1, 7}, {1, 7, 11}, {1, 7, 11, 14}, {1, 7, 13}, {1, 7, 13, 14}, {1, 7, 13, 14, 15}, {1, 7, 13, 15}, {1, 7, 14}, {1, 7, 14, 15}, {1, 7, 15}, {1, 11}, {1, 11, 14}, {1, 13}, {1, 13, 14}, {1, 13, 14, 15}, {1, 13, 15}, {1, 14}, {1, 14, 15}, {1, 15}, {2, 3}, {2, 3, 12}, {2, 3, 12, 13}, {2, 3, 13}, {2, 3, 13, 14}, {2, 3, 13, 14, 15}, {2, 3, 13, 15}, {2, 3, 14}, {2, 3, 14, 15}, {2, 3, 15}, {2, 9}, {2, 9, 12}, {2, 9, 12, 13}, {2, 9, 13}, {2, 9, 13, 14}, {2, 9, 13, 14, 15}, {2, 9, 13, 15}, {2, 9, 14}, {2, 9, 14, 15}, {2, 9, 15}, {2, 12}, {2, 12, 13}, {2, 13}, {2, 13, 14}, {2, 13, 14, 15}, {2, 13, 15}, {2, 14}, {2, 14, 15}, {2, 15}, {3, 4}, {3, 4, 5}, {3, 4, 5, 10}, {3, 4, 5, 11}, {3, 4, 5, 11, 14}, {3, 4, 5, 12}, {3, 4, 5, 12, 13}, {3, 4, 5, 13}, {3, 4, 5, 13, 14}, {3, 4, 5, 13, 14, 15}, {3, 4, 5, 13, 15}, {3, 4, 5, 14}, {3, 4, 5, 14, 15}, {3, 4, 5, 15}, {3, 4, 8}, {3, 4, 8, 10}, {3, 4, 8, 11}, {3, 4, 8, 11, 14}, {3, 4, 8, 12}, {3, 4, 8, 12, 13}, {3, 4, 8, 13}, {3, 4, 8, 13, 14}, {3, 4, 8, 13, 14, 15}, {3, 4, 8, 13, 15}, {3, 4, 8, 14}, {3, 4, 8, 14, 15}, {3, 4, 8, 15}, {3, 4, 10}, {3, 4, 11}, {3, 4, 11, 14}, {3, 4, 12}, {3, 4, 12, 13}, {3, 4, 13}, {3, 4, 13, 14}, {3, 4, 13, 14, 15}, {3, 4, 13, 15}, {3, 4, 14}, {3, 4, 14, 15}, {3, 4, 15}, {3, 5}, {3, 5, 7}, {3, 5, 7, 10}, {3, 5, 7, 11}, {3, 5, 7, 11, 14}, {3, 5, 7, 12}, {3, 5, 7, 12, 13}, {3, 5, 7, 13}, {3, 5, 7, 13, 14}, {3, 5, 7, 13, 14, 15}, {3, 5, 7, 13, 15}, {3, 5, 7, 14}, {3, 5, 7, 14, 15}, {3, 5, 7, 15}, {3, 5, 10}, {3, 5, 11}, {3, 5, 11, 14}, {3, 5, 12}, {3, 5, 12, 13}, {3, 5, 13}, {3, 5, 13, 14}, {3, 5, 13, 14, 15}, {3, 5, 13, 15}, {3, 5, 14}, {3, 5, 14, 15}, {3, 5, 15}, {3, 6}, {3, 6, 12}, {3, 6, 12, 13}, {3, 6, 13}, {3, 6, 13, 14}, {3, 6, 13, 14, 15}, {3, 6, 13, 15}, {3, 6, 14}, {3, 6, 14, 15}, {3, 6, 15}, {3, 7}, {3, 7, 8}, {3, 7, 8, 10}, {3, 7, 8, 11}, {3, 7, 8, 11, 14}, {3, 7, 8, 12}, {3, 7, 8, 12, 13}, {3, 7, 8, 13}, {3, 7, 8, 13, 14}, {3, 7, 8, 13, 14, 15}, {3, 7, 8, 13, 15}, {3, 7, 8, 14}, {3, 7, 8, 14, 15}, {3, 7, 8, 15}, {3, 7, 10}, {3, 7, 11}, {3, 7, 11, 14}, {3, 7, 12}, {3, 7, 12, 13}, {3, 7, 13}, {3, 7, 13, 14}, {3, 7, 13, 14, 15}, {3, 7, 13, 15}, {3, 7, 14}, {3, 7, 14, 15}, {3, 7, 15}, {3, 8}, {3, 8, 10}, {3, 8, 11}, {3, 8, 11, 14}, {3, 8, 12}, {3, 8, 12, 13}, {3, 8, 13}, {3, 8, 13, 14}, {3, 8, 13, 14, 15}, {3, 8, 13, 15}, {3, 8, 14}, {3, 8, 14, 15}, {3, 8, 15}, {3, 10}, {3, 11}, {3, 11, 14}, {3, 12}, {3, 12, 13}, {3, 13}, {3, 13, 14}, {3, 13, 14, 15}, {3, 13, 15}, {3, 14}, {3, 14, 15}, {3, 15}, {4, 5}, {4, 5, 9}, {4, 5, 9, 10}, {4, 5, 9, 11}, {4, 5, 9, 11, 14}, {4, 5, 9, 12}, {4, 5, 9, 12, 13}, {4, 5, 9, 13}, {4, 5, 9, 13, 14}, {4, 5, 9, 13, 14, 15}, {4, 5, 9, 13, 15}, {4, 5, 9, 14}, {4, 5, 9, 14, 15}, {4, 5, 9, 15}, {4, 5, 10}, {4, 5, 11}, {4, 5, 11, 14}, {4, 5, 12}, {4, 5, 12, 13}, {4, 5, 13}, {4, 5, 13, 14}, {4, 5, 13, 14, 15}, {4, 5, 13, 15}, {4, 5, 14}, {4, 5, 14, 15}, {4, 5, 15}, {4, 8}, {4, 8, 9}, {4, 8, 9, 10}, {4, 8, 9, 11}, {4, 8, 9, 11, 14}, {4, 8, 9, 12}, {4, 8, 9, 12, 13}, {4, 8, 9, 13}, {4, 8, 9, 13, 14}, {4, 8, 9, 13, 14, 15}, {4, 8, 9, 13, 15}, {4, 8,

9, 14}, {4, 8, 9, 14, 15}, {4, 8, 9, 15}, {4, 8, 10}, {4, 8, 11}, {4, 8, 11, 14}, {4, 8, 12}, {4, 8, 12, 13}, {4, 8, 13}, {4, 8, 13, 14}, {4, 8, 13, 14, 15}, {4, 8, 13, 15}, {4, 8, 14}, {4, 8, 14, 15}, {4, 8, 15}, {4, 9}, {4, 9, 10}, {4, 9, 11}, {4, 9, 11, 14}, {4, 9, 12}, {4, 9, 12, 13}, {4, 9, 13}, {4, 9, 13, 14}, {4, 9, 13, 14, 15}, {4, 9, 13, 15}, {4, 9, 14}, {4, 9, 14, 15}, {4, 9, 15}, {4, 10}, {4, 11}, {4, 11, 14}, {4, 12}, {4, 12, 13}, {4, 13}, {4, 13, 14}, {4, 13, 14, 15}, {4, 13, 15}, {4, 14}, {4, 14, 15}, {4, 15}, {5, 7}, {5, 7, 9}, {5, 7, 9, 10}, {5, 7, 9, 11}, {5, 7, 9, 11, 14}, {5, 7, 9, 12}, {5, 7, 9, 12, 13}, {5, 7, 9, 13}, {5, 7, 9, 13, 14}, {5, 7, 9, 13, 14, 15}, {5, 7, 9, 13, 15}, {5, 7, 9, 14}, {5, 7, 9, 14, 15}, {5, 7, 9, 15}, {5, 7, 10}, {5, 7, 11}, {5, 7, 11, 14}, {5, 7, 12}, {5, 7, 12, 13}, {5, 7, 13}, {5, 7, 13, 14}, {5, 7, 13, 14, 15}, {5, 7, 13, 15}, {5, 7, 14}, {5, 7, 14, 15}, {5, 7, 15}, {5, 9}, {5, 9, 10}, {5, 9, 11}, {5, 9, 11, 14}, {5, 9, 12}, {5, 9, 12, 13}, {5, 9, 13}, {5, 9, 13, 14}, {5, 9, 13, 14, 15}, {5, 9, 13, 15}, {5, 9, 14}, {5, 9, 14, 15}, {5, 9, 15}, {5, 10}, {5, 11}, {5, 11, 14}, {5, 12}, {5, 12, 13}, {5, 13}, {5, 13, 14}, {5, 13, 14, 15}, {5, 13, 15}, {5, 14}, {5, 14, 15}, {5, 15}, {6, 9}, {6, 9, 12}, {6, 9, 12, 13}, {6, 9, 13}, {6, 9, 13, 14}, {6, 9, 13, 14, 15}, {6, 9, 13, 15}, {6, 9, 14}, {6, 9, 14, 15}, {6, 9, 15}, {6, 12}, {6, 12, 13}, {6, 13}, {6, 13, 14}, {6, 13, 14, 15}, {6, 13, 15}, {6, 14}, {6, 14, 15}, {6, 15}, {7, 8}, {7, 8, 9}, {7, 8, 9, 10}, {7, 8, 9, 11}, {7, 8, 9, 11, 14}, {7, 8, 9, 12}, {7, 8, 9, 12, 13}, {7, 8, 9, 13}, {7, 8, 9, 13, 14}, {7, 8, 9, 13, 14, 15}, {7, 8, 9, 13, 15}, {7, 8, 9, 14}, {7, 8, 9, 14, 15}, {7, 8, 9, 15}, {7, 8, 10}, {7, 8, 11}, {7, 8, 11, 14}, {7, 8, 12}, {7, 8, 12, 13}, {7, 8, 13}, {7, 8, 13, 14}, {7, 8, 13, 14, 15}, {7, 8, 13, 15}, {7, 8, 14}, {7, 8, 14, 15}, {7, 8, 15}, {7, 9}, {7, 9, 10}, {7, 9, 11}, {7, 9, 11, 14}, {7, 9, 12}, {7, 9, 12, 13}, {7, 9, 13}, {7, 9, 13, 14}, {7, 9, 13, 14, 15}, {7, 9, 13, 15}, {7, 9, 14}, {7, 9, 14, 15}, {7, 9, 15}, {7, 10}, {7, 11}, {7, 11, 14}, {7, 12}, {7, 12, 13}, {7, 13}, {7, 13, 14}, {7, 13, 14, 15}, {7, 13, 15}, {7, 14}, {7, 14, 15}, {7, 15}, {8, 9}, {8, 9, 10}, {8, 9, 11}, {8, 9, 11, 14}, {8, 9, 12}, {8, 9, 12, 13}, {8, 9, 13}, {8, 9, 13, 14}, {8, 9, 13, 14, 15}, {8, 9, 13, 15}, {8, 9, 14}, {8, 9, 14, 15}, {8, 9, 15}, {8, 10}, {8, 11}, {8, 11, 14}, {8, 12}, {8, 12, 13}, {8, 13}, {8, 13, 14}, {8, 13, 14, 15}, {8, 13, 15}, {8, 14}, {8, 14, 15}, {8, 15}, {9, 10}, {9, 11}, {9, 11, 14}, {9, 12}, {9, 12, 13}, {9, 13}, {9, 13, 14}, {9, 13, 14, 15}, {9, 13, 15}, {9, 14}, {9, 14, 15}, {9, 15}, {11, 14}, {12, 13}, {13, 14}, {13, 14, 15}, {13, 15}, {14, 15}

0.13 Transitions out of each state in the two-unit system

{18} → {3}, {4}, {5}, {7}, {8}, {9}, {13}, {14}, {15}
{0} → {1}, {2}, {0, 13}, {0, 14}, {0, 15}, {6, 9}
{1} → {0}, {3}, {5}, {1, 4}, {1, 7}, {1, 13}, {1, 14}, {1, 15}
{2} → {0}, {4}, {5}, {2, 3}, {2, 9}, {2, 13}, {2, 14}, {2, 15}
{3} → {1}, {18}, {3, 4}, {3, 5}, {3, 7}, {3, 8}, {3, 13}, {3, 14}, {3, 15}
{4} → {2}, {18}, {3, 4}, {4, 5}, {4, 8}, {4, 9}, {4, 13}, {4, 14}, {4, 15}
{5} → {1}, {2}, {18}, {3, 5}, {4, 5}, {5, 7}, {5, 9}, {5, 13}, {5, 14}, {5, 15}
{6} → {7}, {8}, {3, 6}, {6, 9}, {6, 13}, {6, 14}, {6, 15}
{7} → {6}, {18}, {3, 7}, {5, 7}, {7, 8}, {7, 9}, {7, 13}, {7, 14}, {7, 15}
{8} → {6}, {18}, {3, 8}, {4, 8}, {7, 8}, {8, 9}, {8, 13}, {8, 14}, {8, 15}
{9} → {18}, {4, 9}, {5, 9}, {7, 9}, {8, 9}, {9, 13}, {9, 14}, {9, 15}
{10} → {11}, {12}, {3, 10}, {4, 10}, {5, 10}, {7, 10}, {8, 10}, {9, 10}
{11} → {10}, {13}, {15}, {3, 11}, {4, 11}, {5, 11}, {7, 11}, {8, 11}, {9, 11}, {11, 14}
{12} → {10}, {14}, {15}, {3, 12}, {4, 12}, {5, 12}, {7, 12}, {8, 12}, {9, 12}, {12, 13}
{13} → {11}, {18}, {3, 13}, {4, 13}, {5, 13}, {7, 13}, {8, 13}, {9, 13}, {13, 14}, {13, 15}
{14} → {12}, {18}, {3, 14}, {4, 14}, {5, 14}, {7, 14}, {8, 14}, {9, 14}, {13, 14}, {14, 15}
{15} → {11}, {12}, {18}, {3, 15}, {4, 15}, {5, 15}, {7, 15}, {8, 15}, {9, 15}, {13, 15}, {14, 15}
{0, 13} → {1, 13}, {2, 13}, {0}, {0, 13, 14}, {0, 13, 15}, {6, 9, 13}
{0, 13, 14} → {1, 13, 14}, {2, 13, 14}, {0, 14}, {0, 13}, {0, 13, 14, 15}, {6, 9, 13, 14}
{0, 13, 14, 15} → {1, 13, 14, 15}, {2, 13, 14, 15}, {0, 14, 15}, {0, 13, 15}, {0, 13, 14}, {6, 9, 13, 14, 15}
{0, 13, 15} → {1, 13, 15}, {2, 13, 15}, {0, 15}, {0, 13}, {0, 13, 14, 15}, {6, 9, 13, 15}
{0, 14} → {1, 14}, {2, 14}, {0}, {0, 13, 14}, {0, 14, 15}, {6, 9, 14}
{0, 14, 15} → {1, 14, 15}, {2, 14, 15}, {0, 15}, {0, 14}, {0, 13, 14, 15}, {6, 9, 14, 15}
{0, 15} → {1, 15}, {2, 15}, {0}, {0, 13, 15}, {0, 14, 15}, {6, 9, 15}
{1, 4} → {3, 4}, {4, 5}, {1}, {1, 4, 13}, {1, 4, 14}, {1, 4, 15}
{1, 4, 11} → {3, 4, 11}, {4, 5, 11}, {1, 11}, {1, 4, 13}, {1, 4, 15}, {1, 4, 11, 14}
{1, 4, 11, 14} → {3, 4, 11, 14}, {4, 5, 11, 14}, {1, 11, 14}, {1, 4, 13, 14}, {1, 4, 14, 15}, {1, 4, 11}
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