

Molecular Combustion Motors

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We construct a molecular model of an internal combustion engine, by coupling a Brownian ratchet with an exothermic chemical cycle. We derive explicitly the thermodynamically allowed couplings, and show that almost every such coupling will result in motion. We compute from this formalism the maximal transmission efficiency of Brownian gears.

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Cells have a service infrastructure, just like cities have steam tunnels and subways and trucks delivering food to supermarkets. There are several related aspects to this infrastructure. Various substances have to be shipped from the place where they are produced to the place where they are needed. This involves transporting them both within regions of the cells and across regions [1,2]. Within a region, transport is achieved, for instance, through protein motors which walk on a complex and dynamic set of highways (the cytoskeleton), and can pull along vesicles containing those substances. The motors consume energy-carrying molecules (adenosine triphosphate or ATP) to walk.

These motors are extraordinarily tiny: the motor domain of kinesin is about 12 nm across, about 50 times smaller than the smallest transistor we can manufacture on microchips. Their length scale and energy scale reveal they are essentially Brownian machines. In this Letter, I will try to outline a mathematical framework with which one can describe how a Brownian machine can convert chemical energy into mechanical motion.

A little over 30 years ago, Feynman described a Brownian motor which has been the basis of many models [3]. A paddle sits in a box with gas at a certain temperature and is subject to Brownian fluctuations. The paddle is coupled to a ratchet device which, supposedly, should "rectify" these fluctuations to provide motile power. The ratchet sits in a box at some other temperature and can itself random walk. Feynman shows that this contraption obeys precisely the formulas for a Carnot cycle, so it is a Brownian analog of a steam engine. Since then, several models formally related to the Feynman ratchet have been applied to microscopic systems. Fox described rotary molecular assemblers [4], Vale and Oosawa tried to use a Feynman ratchet to describe protein motors [5], Oster and co-workers studied polymerization ratchets [6,7], Simon *et al.* understood protein translocation across membranes [8], and Ajdari and Prost proposed a setup for high performance chromatography by showing that periodically turning a ratchetlike potential on and off will generate transport [9]. Recently I observed that a ratchet can rectify nonequilibrium fluctuations to generate motion, even if the fluctuations are symmetric [10]; I argued this only for low frequency fluctuations, but Do-

ering *et al.* have made more detailed and rigorous studies [11] which show the phenomenon to persist at high frequencies, and which have also uncovered other very interesting phenomena; Millonas and Dykman have introduced powerful techniques for this case [12]. Stochastic variants of the Ajdari-Prost setup have also been studied very recently [13–15], also in connection with protein motor dynamics.

The setup in [10] did not quite present a full motor, rather just one half of a motor; the relationship between the nonequilibrium fluctuations and the fact that ATP carries energy was not explored and this will be one of my goals now. Protein motors obtain energy from the degradation of ATP. The energy (about $12kT$) is stored in a phosphate bond, and is released when this bond is broken, to form ADP (adenosine diphosphate) and P_i (inorganic phosphate). The motor continuously "breaks" ATP molecules in a never-ending cycle, somewhat like a machine gun "breaking" bullets. First, we just have the motor M ; then an ATP is bound to the motor, to get $M \times \text{ATP}$; then ATP is hydrolyzed to get $M \times \text{ADP} \times P_i$; then the phosphate is released $M \times \text{ADP}$ and then the ADP is released, so we get back to the initial state M . Different motors may operate with different cycles, and biologists have been painstakingly performing experiments to elucidate the details of the cycle for each motor [16].

I have described this cycle as going one way. But we know that all reactions are reversible, that reaction "arrows" always go both ways; we also know that the quotient of the forward arrow over the backward arrow equals the exponential of the Gibbs free energy gained in the reaction, divided by thermal energy. In a reaction like $\text{ATP} \rightleftharpoons \text{ADP} \times P_i$, this quotient is approximately $e^{12} \approx 10^5$, so drawing the arrow as going one way seems reasonable. The other transitions are more delicate. The power plants in the cell are constantly removing all of the used ADPs and P_i s, and supplying fresh new ATP. If these energy factories were turned off, then eventually the concentration of ATP would drop to its equilibrium, one ATP per e^{12} ADPs. However, under physiologic conditions there are about 10 ATPs per ADP, and it is the energy factories' job to keep it that way. So, the release of phosphates and ADPs from the motor is an entropically

favorable process because their concentration outside the motor is being kept below equilibrium by 6 decades. *The chemical cycle loops one way as a direct consequence of far-from-equilibrium concentrations of the reactants involved*; it loops in the direction in which the reaction proceeds towards equilibrium.

A cycle which does not gain Gibbs free energy by going around will just random walk through the graph in an unbiased fashion, and will generate Poissonian (time-independent) events. A cycle which does gain free energy will traverse the cycle in a specific sequence, and will generate non-Poissonian (time-correlated) events. Consider for instance two Markov graphs, $A \rightleftharpoons B \rightleftharpoons C \rightleftharpoons A$ and $A \rightarrow B \rightarrow C \rightarrow A$. Assume the first one to be unbiased, so that it can move back and forth with the same rates; it will generate Poissonian events because there are many trajectories and each one sets a time scale. The second graph accepts just one trajectory and hence there is one privileged time scale, that for going around the graph [17]. It is straightforward but tedious to show by direct path counting that a cycle will generate Poissonian events if and only if the rates for going around in each direction are balanced, i.e., if there is no free energy gained by going around. If $\Delta G \neq 0$, detailed balance is lost and the cycle generates time-correlated, nonequilibrium fluctuations.

So we have the ingredients necessary to build a motor. The ratchet described in [10] is a little Brownian machine that eats nonequilibrium fluctuations and walks; a chemical cycle is a little Brownian machine that eats chemical energy and generates nonequilibrium fluctuations. If we glue them together, we get a machine which eats chemical energy and walks, a Brownian version of an internal combustion engine, so molecular it "burns" one molecule of "fuel" at a time.

But to glue these two machines we require a minimum of care. We can remember that Kramers [18] described chemical reactions precisely through Langevin equations to derive the theory of chemical kinetics. Kramers only described a single reaction event, but the adaptation to a cycle spells itself out. Instead of a discrete state, we will have a continuous "reaction coordinate" x , which, for a cycle, must be a variable on the circle. We will have a potential $V(x)$ stating what the Gibbs free energy corresponding to each value of the reaction coordinate is; each minimum of the potential corresponds to a vertex on the graph. However, as we go around the circle, we have gained ΔG free energy, so that the potential is steadily tilted. We have just mapped the chemical cycle to a steadily tilted ratchet, as described in [10]; the Fokker-Planck equation (FPE) associated to any such process can be solved in double quadratures for any arbitrary potential [17]; the current J is given by

$$\frac{kT(e^{\frac{\Delta G}{kT}} - 1)}{J} = \oint \oint e_{kT}^{V(x') - V(x) + \Delta G \Theta(x' - x)} dx' dx,$$

where $e_{kT}^x \equiv \exp(x/kT)$ and Θ is the Heaviside step.

We have now to define the proper way to couple these cycles. We have both cycles, mechanical and chemical, described by an identical framework. Calling x the chemical coordinate, and y the spatial coordinate, we have

$$\dot{x} = f_x(x, y) + \xi(t), \quad \dot{y} = f_y(x, y) + \chi(t), \quad (1)$$

where $x, y \in S^1$, $\langle \xi(t)\xi(s) \rangle = \langle \chi(t)\chi(s) \rangle = 2kT\delta(s - t)$, and $\langle \chi(t)\xi(s) \rangle = 0$. (This is in essence a continuous version of Hill cycles [19]; Astumian and Biers have independently argued for a similar description [13].)

We have thus a Langevin equation on a torus. As long as we are on a small portion of the torus (i.e., the motor is burning *one* specific molecule of fuel) we must uphold the first law. This is done by requesting that the system be *locally conservative*, i.e., that the vector field $\mathbf{f}$ be curl free. The system ceases to be conservative on the global scale (when we traverse a full loop of the chemistry), because consecutive cycles act by breaking *different* molecules of ATP rather than the same molecule.

In Euclidean space the curl-free condition ensures that the line integral of $\mathbf{f}$ around any closed loop is zero. On the torus, this will be true in general only for those loops which are homotopic to a point. There are loops which go *around* the torus and do not cut it into two different pieces, and for these loops the integral will generically be nonzero. More technically, $\mathbf{f}$ is a *1-form which is closed but not exact* [20]. What the curl-free condition does imply is that the integral around a loop is the same for any two loops which are homotopic; this integral is thus a function of the homotopy class only. Homotopy classes form a group generated by the two loops which go around x and y (respectively) exactly once. The integral is additive under the group operation, so it suffices to specify this integral on the two generating loops to specify it for all loops.

In order to model a motor moving freely under no external loads, the correct value on the two generating loops must be set as follows. We do not have any bias in the mechanical part, and therefore a loop going around the mechanical cycle once and not around the chemistry (i.e., the motor slides one step without consuming fuel) must gain zero energy. A loop going once around the chemistry and zero times in the mechanics has to gain precisely the Gibbs free energy set by the chemistry. Thus, the integral of the vector field around any loop going through the chemistry once will be the same regardless of whether it advanced in space or not. This is an important self-consistency fact of the formalism: the free energy gained by burning fuel does not depend upon whatever happened mechanically, as it should, since this energy is a function solely of ATP hydrolyzation energy and the concentrations of ATP, ADP, and P_i and therefore should not depend upon any mechanical variable.

What will depend upon the mechanics is the *rate* at which the motor consumes fuel. Once we decide how to couple the chemistry to the mechanics, then the curl-free condition for the vector field determines *uniquely*

the “backcoupling” from the mechanics to the chemistry. Thus the state of motion of the motor determines how fast fuel is being consumed, just like in a car’s motor. Any given model based upon this formalism predicts (and is therefore obliged to fit) two measurements at once: how fast the motor moves, and how fast it consumes ATP.

The general image of such a motor operating might be that of dragging a particle through a periodic landscape, with a force in a certain direction. If the mountains of the landscape are lopsided, then the particle will show a systematic drift in the transverse direction.

What we will be wanting to solve is the stationary FPE:

$$\nabla \cdot \mathbf{J} = 0, \quad \mathbf{J} = \mathbf{f}P - kT\nabla P, \quad (2)$$

where $\mathbf{f}$ is as above. What we want to compute from the solution to this equation are the rates for going around the mechanics (the average speed of the motor) and for going around the chemistry (the mean hydrolyzation rate of ATP). These are obtained as surface integrals: Given a surface normal to the chemistry dimension (a loop around the mechanics in this case), the surface integral of the normal component of the current will tell us the rate of ATP hydrolysis. Because the current is divergence-free, these rates are independent of the surfaces in question and only depend upon their homotopy class.

If for some given $\mathbf{f}$ there is a nonzero mean speed of the motor, we have, effectively, transduction of chemical energy into mechanical motion and thus a working motor. I will now show that almost any coupling will do; of course, different couplings may have widely different efficiencies.

The mean speed equals the integral of the y component of the current along a loop in the x direction. Let us first establish under which conditions this y component might be strictly zero everywhere. Since

$$J_y = f_y(x, y)P(x, y) - kT\partial_y P(x, y) = 0,$$

we see that $P(x, y)$ can be obtained from $P(x, 0)$ through integration of a linear first order ordinary differential equation (where x is playing the role of a parameter). So

$$P(x, y) = P(x, 0)e^{\int_0^y dy' f_y(x, y')/kT}.$$

Calling $Q(x) = P(x, 0)$ and $R(x, y)$ the exponential, and remembering that $\partial_x f_y = \partial_y f_x$, we obtain

$$\partial_x P = Q'R + QR \frac{f_x(x, y) - f_x(x, 0)}{kT}$$

so that the Fokker-Planck equation reads now

$$\partial_x J_x = \partial_x [f_x(x, 0)QR - kTQ'R] = 0. \quad (3)$$

Evaluating this equation at $y = 0$, when $R \equiv 1$, we get that $Q = P(x, 0)$ satisfies a one-dimensional Fokker-Planck equation

$$\partial_x [f_x(x, 0)P(x, 0) - kT\partial_x P(x, 0)] = \partial_x J^0 = 0$$

which we can solve analytically; $J^0 \equiv f_x(x, 0)P(x, 0) - kT\partial_x P(x, 0)$ is thus a constant. But then Eq. (3) can be rewritten as

$$\partial_x [f_x(x, 0)QR - kTQ'R] = \partial_x (J^0 R) = J^0 \partial_x R = 0.$$

We know $J^0 \neq 0 \iff \Delta G \neq 0$; if so, then $\partial_x R \equiv 0$, which implies that $\partial_x f_y \equiv \partial_y f_x \equiv 0$. So the x and y degrees of freedom are uncoupled. We have just proven that if x and y are coupled, the y component of the current cannot be everywhere zero. The mean speed of the motor might still cancel out, since it is an integral of this current.

This integral might cancel due to parity symmetry, or perhaps due to an “accidental” cancellation. But this integral is the same for every curve homotopic to a horizontal slice, so accidental cancellations cannot be structurally stable. Thus, as soon as we have symmetry breaking in space, almost every coupling between space and chemistry (and a driving force along the chemistry direction) will produce a working motor.

But then we have to worry about the efficiency of such a motor. The most important theoretical result to be obtained should be a maximal efficiency calculation, in the sense of Carnot. There is a trivial class of vector fields for which this can be done explicitly. We can always write the force field $\mathbf{f}$ as

$$\mathbf{f} = \nabla U(x, y) + (F, 0),$$

i.e., as the gradient of a potential plus a constant force in the x direction. If $U(x, y) \equiv V(ax - by)$ with a and b integers, and $V(z)$ a periodic function, we have the Brownian equivalent of two coupled gears, where V is the “shape” of one tooth, and a and b are the number of teeth in each gear. By applying a force to one gear we make the other one move. It is evident that thermal noise will allow the gears to slide over each other, not unlike actual engine transmissions coupling through transmission fluid before the teeth actually lock. The 2D FPE for this potential reduces immediately to a 1D FPE which can be solved analytically, because the structure of the equation requires that P be of the form $P(ax - by)$, too. Calling $\alpha = a/(a^2 + b^2)$, the 1D FPE is

$$\nabla \cdot \mathbf{J} = (a^2 + b^2) \{ (V' + \alpha F)P - kTP' \}' = 0.$$

$K = (V' + \alpha F)P - kTP'$ is a constant which we can compute as above. The total rates are

$$R_x = \oint J_x dy = \frac{b^2}{a^2 + b^2} F + aK,$$

$$R_y = \oint J_y dx = \frac{ab}{a^2 + b^2} F - bK.$$

The first terms are purely geometrical and classical; the second terms are Brownian and represent the losses due

to the ability of the gears to slide against each other. So we have an explicit example on which to compute efficiencies. The answer depends, as usual, on what is being maximized, and this is something we have to keep in mind whenever thinking of the "efficiency of a motor protein."

For simplicity let us do this at $kT = 0$, since gears move classically, but let us keep the motor terminology: R_x is the rate of ATP consumption and R_y is the mean speed of the motor. If we want to maximize the number of steps per ATP (R_y/R_x), then we should choose $a/b \rightarrow \infty$; the motor moves an arbitrarily large number of steps per single ATP, but $R_y \rightarrow 0$. If we want to maximize the speed R_y , then we choose $a = b$. If we want to maximize the "stall load" (not present above but easily computable), then we want $b/a \rightarrow \infty$. From this trivial example we see very clearly that to speak about efficiency of motors we have to define what is being optimized.

For less artificial cases, it is easy to see that when the coupling between x and y is small we recover both the ratchets of [9] and [10]. In this case we can write $\mathbf{f} = -\nabla V$ with $V(x, y) = V_1(x) + V_2(y) - Fx + \epsilon W(x, y)$. So,

$$\begin{aligned}\dot{x} &= -\partial_x V_1(x) + F - \epsilon \partial_x W(x, y) + \xi(t), \\ \dot{y} &= -\partial_y V_2(y) - \epsilon \partial_y W(x, y) + \chi(t).\end{aligned}\quad (4)$$

Because for $\epsilon = 0$ there is no J_y but there is a J_x , for small ϵ we can (to lowest order) neglect the influence of y on x , and thus we have a unidirectional coupling from x to y ; since x is (on average) steadily increasing like $x \approx J_x t$, a function such as $\cos(x)$ looks like $\cos(J_x t)$ plus higher frequencies. Hence, if we have a coupling like $W(x, y) = [1 + \cos(x)]V_2(y)$, we recover a fluctuating potential like in [9], and for $W = \cos(x + y)$ we recover the forced ratchet of [10]. Since J_x is (for $\epsilon = 0$) a convex function of F , the backcoupling would always increase the rate of ATP consumption as expected. This argument can be made precise through using a change of variables $z(x) = \int_0^x P(x') dx'$, but the details are not interesting.

What I have presented is not a model of motor proteins, but a framework for building models of a single motor. The virtues of this framework are basically two. First, many models in biology are stated in terms of what the model *does*; this is rather disturbing since then we cannot know whether the model works because of real virtues or because of construction. Here, the model just states the energy associated to all combinations of the chemical and mechanical states, and what the model does is obtained by solving the equations. Second, this framework does by itself all the delicate bookkeeping of the first law, which eliminates the possibility of a motor moving by plain bootstrapping; i.e., perpetual motion machines, no matter how subtly disguised, are forbidden.

The framework assumes a single motor. In order to model several motors working together the proper proce-

dure might be to overlay the statistical analysis of Leibler and Huse [16] on top of this single-motor analysis.

There are two implicit assumptions. First, that the degrees of freedom of the protein are cleanly separated into fast and slow; the latter (plus the chemical state) form the phase space, and the former just dress the energy landscape. Second, the two-dimensional cases we have formulated above can be extended to a higher dimensional space if the additional slow degrees of freedom do not form a manifold with a non-Abelian cohomology.

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