unsatisfactory for both systems, because a likelihood ratio test strongly favors the model with migration limitation in both cases [for Amazon: $\chi^2 = 24.6$, 1 degree of freedom (d.f.), $P < 0.001$; for CFR: $\chi^2 = 19.4$, 1 d.f., $P < 0.001$].

Estimates of Θ can be converted to estimates of per capita speciation rate if it is possible to estimate the number of individuals in the metacommunity. With a much larger area, the Amazon rain forest metacommunity almost certainly contains at least as many individuals as does fynbos, which covers <50,000 km^2. The high estimates for Θ thus imply a substantially higher per capita speciation rate in the CFR. These results are consistent with the prevailing view that the western CFR is an extremely migration-limited system with extraordinarily high speciation rates. Each of the local communities in our data set is an identifiable subregion of the CFR that consists of a range of hills or mountains and adjacent lowlands. Thus, the CFR metacommunity is topographically fragmented, which predicts low migration rates, consistent with our results. With these low migration rates, it is likely that local communities will be sufficiently isolated to allow ecological drift to cause divergence among communities, because few individuals per generation will be exchanged (*19*). Further, populations of individual species will be genetically isolated, so that genetic drift will tend to cause divergence and the formation of new species. Thus, our results support the view that the fynbos metacommunity consists of topographical islands isolated not by water but by drier lowlands. This pattern contrasts sharply with that found in tropical rain forests, which exhibit high connectivity over long distances. Within the CFR, the association of the highest values of Θ, and thus speciation rates, with the lowest migration rates supports the view that isolation over short spatial scales (1 to 100 km) has played a role in generating, as well as structuring, the high diversity of the CFR.

References and Notes

1. H. P. Linder, C. R. Hardy, *Philos. Trans. R. Soc. London Ser. B* **359**, 1623 (2004).
2. P. Goldblatt, J. Manning, *Cape Plants: A Conspectus of the Cape Flora of South Africa* (National Botanical Institute of South Africa, Cape Town, 2000).
3. J. E. Richardson *et al.*, *Nature* **412**, 181 (2001).
4. S. P. Hubbell, *The Unified Neutral Theory of Biodiversity and Biogeography* (Princeton Univ. Press, Princeton, 2001).
5. R. M. Cowling, P. W. Rundel, B. B. Lamont, M. K. Arroyo, M. Arianoutsou, *Trends Ecol. Evol.* **11**, 362 (1996).
6. P. Slingsby, W. J. Bond, *S. Afr. J. Bot.* **51**, 30 (1985).
7. D. J. McDonald, J. M. Juritz, R. M. Cowling, W. J. Knottenbelt, *Plant Syst. Evol.* **195**, 137 (1995).
8. R. H. Whittaker, *Taxon* **21**, 213 (1972).
9. H. ter Steege *et al.*, *Biodiversity Conserv.* **12**, 2255 (2003).
10. N. C. A. Pitman, J. W. Terborgh, M. R. Silman, P. V. Nuñez, *Ecology* **80**, 2651 (1999).
11. N. C. A. Pitman *et al.*, *Ecology* **82**, 2101 (2001).
12. O. J. Hardy, B. Sonké, *For. Ecol. Manage.* **197**, 191 (2004).
13. R. Condit *et al.*, *Science* **295**, 666 (2002).
14. J. Chave, *Ecol. Lett.* **7**, 241 (2004).
15. I. Volkov, J. R. Banavar, S. P. Hubbell, A. Maritan, *Nature* **424**, 1035 (2003).
16. D. Alonso, A. J. McKane, *Ecol. Lett.* **7**, 901 (2004).
17. B. J. McGill, *Nature* **422**, 881 (2003).
18. R. M. Cowling, Ed., *The Ecology of Fynbos: Nutrients, Fire and Diversity* (Oxford Univ. Press, Cape Town, 1992).
19. C. Boucher, *Bothalia* **12**, 455 (1978).
20. H. C. Taylor, *Cederberg Vegetation and Flora* (National Botanical Institute, Cape Town, 1996).
21. B. E. Van Wyk, P. A. Novellie, C. M. Van Wyk, *Bothalia* **18**, 211 (1988).
22. M. J. A. Werger, *Bothalia* **11**, 309 (1974).
23. Materials and methods are available as supporting material on *Science* Online.
24. R. M. Cowling, B. B. Lamont, *Aust. J. Bot.* **46**, 335 (1998).
25. R. M. Cowling, P. M. Holmes, *Biol. J. Linn. Soc.* **47**, 367 (1992).
26. A. Chao, R. L. Chazdon, R. K. Colwell, T.-J. Shen, *Ecol. Lett.* **8**, 148 (2005).
27. R. M. Cowling, S. Proches, in *Plant Diversity and Complexity Patterns. Local, Regional and Global Dimensions*, H. Balslev, Ed. (The Royal Danish Academy of Sciences and Letters, Copenhagen, 2005), vol. 55, pp. 273–288.
28. R. M. Cowling, A. T. Lombard, *Diversity Distr.* **8**, 163 (2002).

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Supporting Online Material

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Generating Electricity While Walking with Loads

Lawrence C. Rome,[1,2]* Louis Flynn,[1] Evan M. Goldman,[1] Taeseung D. Yoo[1]

We have developed the suspended-load backpack, which converts mechanical energy from the vertical movement of carried loads (weighing 20 to 38 kilograms) to electricity during normal walking [generating up to 7.4 watts, or a 300-fold increase over previous shoe devices (20 milliwatts)]. Unexpectedly, little extra metabolic energy (as compared to that expended carrying a rigid backpack) is required during electricity generation. This is probably due to a compensatory change in gait or loading regime, which reduces the metabolic power required for walking. This electricity generation can help give field scientists, explorers, and disaster-relief workers freedom from the heavy weight of replacement batteries and thereby extend their ability to operate in remote areas.

Over the past century, humans have become increasingly dependent on technology, particularly electronic devices. During the past decade, electronic devices have become more mobile, enabling people to use medical, communication, and Global Positioning System (GPS) devices as they move around cities or in the wilderness. At present, all of these devices are powered by batteries, which have a limited energy storage capacity and add considerable weight. Although substantial progress has been made in reducing the power requirements of devices and increasing the power densities of batteries, there has not been a breakthrough in the parallel development of a portable and renewable human-driven energy source (*1*, *2*). The combination of limited energy and the large weight of batteries poses the most critical problem for individuals having high electricity demands in remote areas and who are already carrying heavy loads (such as field scientists or explorers on prolonged expeditions). At present, replacement batteries may make up a substantial proportion (as much as 25%) of the very heavy packs (>36 kg or 80 lbs) that such users must carry (*3*). To help solve this problem, we developed a passive device, the suspended-load backpack, which extracts mechanical energy from the vertical movement of the load during walking and converts it to electricity for powering portable devices.

During terrestrial locomotion, the environment does no work on the body (except for the small force of aerodynamic drag) and conversely, humans do no work on the environment. Rather, almost all of the mechanical work is generated and dissipated inside the body (*4*, *5*). This makes it exceedingly difficult to capture mechanical energy to drive an electrical energy conversion apparatus, because the device would need to be either surgically placed within the body or attached to the outside of the body (such as an exoskeleton), which would affect the person's maneuverability and comfort. Therefore, researchers in the field have focused on putting devices in the only acces-

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[1] Department of Biology, University of Pennsylvania, Philadelphia, PA 19104, USA. [2] Marine Biological Laboratory, Woods Hole, MA 02543, USA.

*To whom correspondence should be addressed. E-mail: lrome@sas.upenn.edu

sible location: the shoe. Such "heel-strike" devices, however, have permitted only small levels of electrical energy generation (10 to 20 mW) (*2*, *6*). The primary reason for this limitation is that on a hard surface, essentially no mechanical work (force times distance) is done at the foot/ground contact point, because under normal circumstances the point of vertical force application does not move in the vertical plane (that is, distance = ~ 0).

Although one can make the shoe compliant so that the foot moves a small distance because of compression of the sole and heel (*7*), this is problematic because increasing compliance leads to declining maneuverability and stability. Although considerable effort has gone into developing exotic energy-generating technologies for shoe devices (*8*), the small magnitude of the mechanical energy source remains a limitation.

We recognized that the vertical movement of a heavy load in the gravitational field during walking represents a heretofore untapped source of mechanical energy and a potential opportunity to generate substantial levels of electricity. During walking, a person moves like an inverted pendulum (*4*, *5*, *9*): One foot is put down and then the body vaults over it, causing the hip to move up and down by 4 to 7 cm (*10*) (Fig. 1). Thus, if one is carrying a load in a backpack, because it is fixed to the body, it has to go up and down the same vertical distance (Fig. 1). A considerable amount of mechanical energy must be transferred (or generated de novo by the muscles) if the load is heavy. In the case of a 36-kg load, 18 J of mechanical energy transfer (or work) accompanies each step (assuming 5 cm displacement), and at two steps s^{-1}, this is equivalent to 35 W. Although this represents a large potential source of mechanical energy, it is also inaccessible if the load is rigidly attached to the body. We reasoned that decoupling the load from the body would allow the differential movement (between the load and the body) necessary for mechanical energy extraction and ultimately electricity production. We therefore designed a device, the suspended-load backpack (Fig. 2), that could be interposed between the body and the load, resulting in differential movement (Fig. 2) and the potential for generating a considerable amount of electrical energy.

Figure 3 shows the displacement and electrical output from the generator of a person walking with a 38-kg load (*11*). In this trial, the relative movement of the load with respect to the pack frame was approximately 4.5 cm (top panel). The linear velocity of the rack, in turn, drove the generator (a 25:1 geared dc motor) up to $\sim$5000 rpm. The middle panel shows the voltage output of the generator. In these experiments, the output of the generator ran through a fixed "load" resistor (25 ohms), and hence the electrical power, calculated as voltage^2/resistance, is shown in the bottom panel. The average electrical power in this trace is 5.6 W. This determination of electrical power was confirmed by joule heating experiments (*11*).

Six male participants walked at speeds ranging from of 4.0 to 6.4 km hour^{-1} (2.5 to 4.0 mph) while carrying 20-, 29-, and 38-kg loads in addition to the fixed portion of the instrumented pack frame, which weighed 5.6 kg (*12*). Average electrical power increased with walking speed and generally increased with the weight of the load in the pack (Fig. 4). Further, while walking up a 10% incline, electrical power generation for a given load and speed was equal to or greater than that on the flat (*13*). The maximum electrical power output obtained on the flat was 7.37 W (±SE = 0.49, n = 6 participants), or about 300 times higher than previously published values gen-

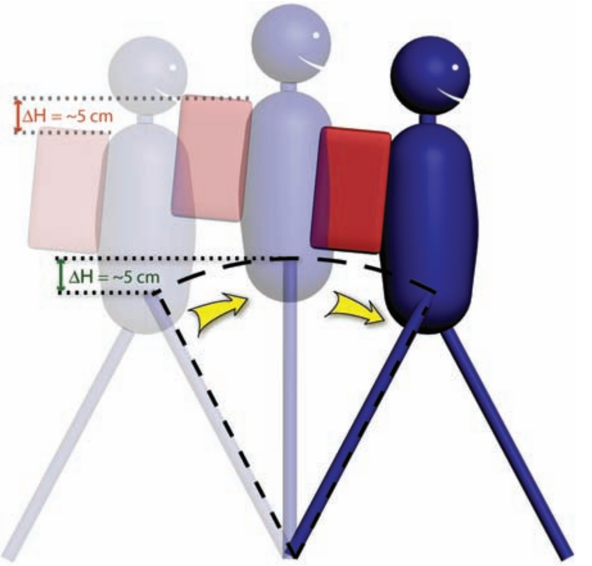

Fig. 1. Humans use an inverted pendulum mode of walking, in which the hip traces out an arc over an extended leg with a vertical excursion (ΔH) of approximately 5 cm. A backpack load rigidly attached to the body would undergo the same vertical excursion. This excursion drives electricity generation.

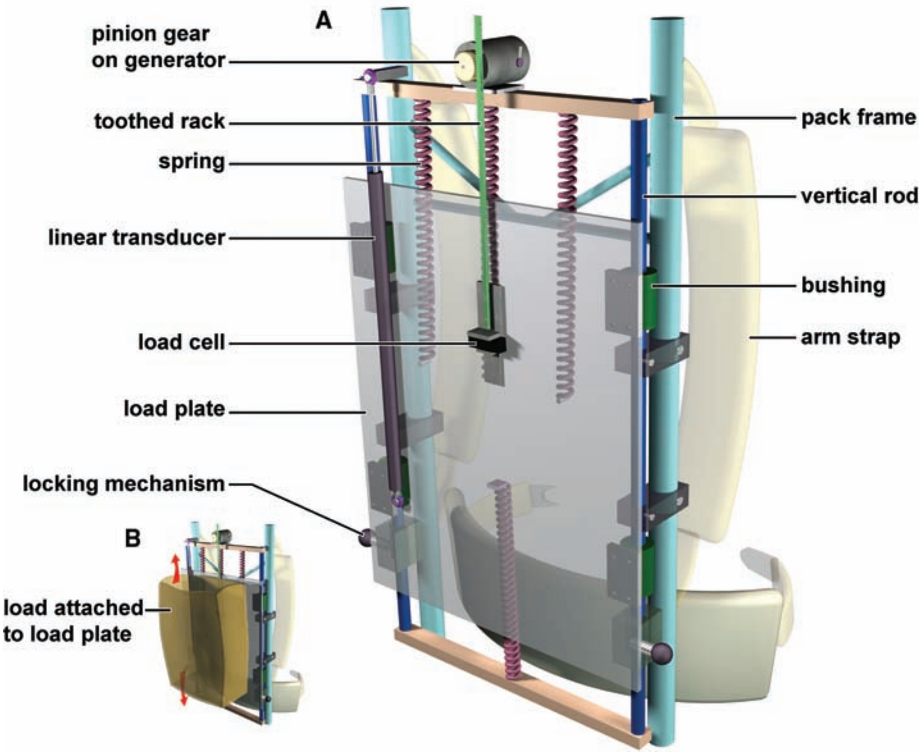

Fig. 2. In the suspended-load backpack, the pack frame is fixed to the body, but the load, mounted on the load plate, is suspended by springs (red) from the frame (blue) (**A**). During walking, the load is free to ride up and down on bushings constrained to vertical rods (**B**) (*11*). Electricity generation was accomplished by attaching a toothed rack to the load plate, which when moving up and down during walking, meshed with a pinion gear mounted on a geared dc motor, functioning as a generator, rigidly attached to the backpack frame.

erated from shoe devices (10 to 20 mW) (*2*, *6*). The mechanical power removed by the generator (and gears) is the product of the average force exerted on the rack (F_{rack}), the displacement of the load with respect to the pack frame (dl_{rack}) (*11*), and the step frequency. Mechanical power into the generator increased with speed and load in a similar fashion as electrical power output. Hence, the efficiency of conversion of mechanical energy to electrical energy (that is, electrical power output divided by mechanical power input) was nearly constant (30 to 40%) over this range of speeds and loads.

To power portable devices (or charge batteries), the alternating polarity of the voltage and current (Fig. 3) must be rectified, which the suspended-load backpack can accomplish with little reduction (~5%) in electrical power output (fig. S1) (*11*). Hence, using circuitry for voltage smoothing, the suspended-load backpack can power multiple devices such as cell phones or GPS receivers, both of which use less than 1 W (*11*).

If generating electricity while wearing the backpack markedly increased metabolic rate, the device would be of limited use. Indeed, one would expect that because mechanical energy is continuously removed from the system by the generator, the muscles would need to perform additional mechanical work during electricity generation in order to replace it. For instance, the mechanical power input to the generator is 12.15 W while walking at 5.6 km hour^{-1} and carrying a 29-kg load (table S3). Because the maximum efficiency of mechanical power production by human muscle is about 25% (*14*, *15*), if the body movement was otherwise the same, one might anticipate a minimum increase of 48.6 W in metabolic power input. We measured the rate of O_2 consumption ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$) of participants walking with the backpack in two configurations: locked (no relative movement, mechanical energy loss, nor electrical energy generation) and unlocked (normal relative movement and electricity generation) in a repeated, paired protocol (*11*) specifically designed to resolve small differences. We found that the metabolic rate increase (Δmetabolic power input) compared to that with the locked backpack was only about 19.1 W (table S1) (*11*), which is much less than would be predicted, providing an "apparent efficiency" of mechanical work production of ~63% (table S3).

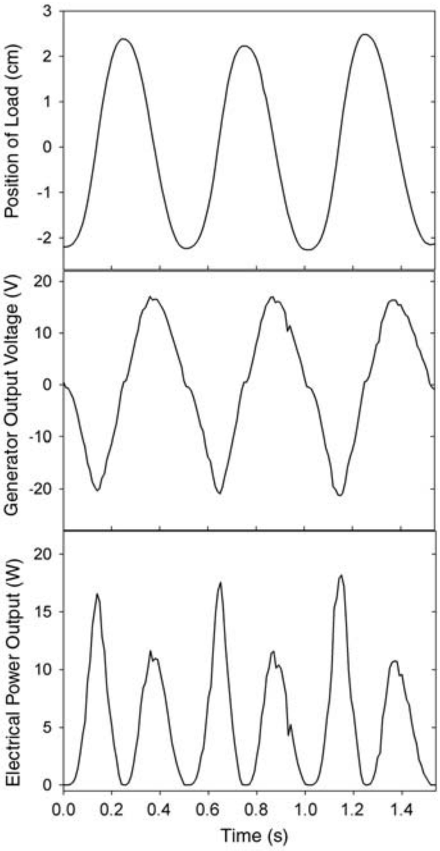

Fig. 3. Position, generator voltage, and electrical power output during walking. In these records, the person is walking with a 38-kg load at 5.6 km hour^{-1}. "Position" refers to the position of the load with respect to the backpack frame, with the midpoint labeled as 0 cm.

On the one hand, these results indicate that electricity can be generated metabolically more cheaply than anticipated. But on the other hand, they suggest that there must be some change in gait or loading regime while walking with the unlocked backpack, which causes a reduction of 29.5 W (48.6 minus 19.1 W) or about 3/5 of the metabolic power required for doing work against the generator. Considerable savings in metabolic cost have been previously reported in African women carrying loads on their heads and attributed to more efficient transfer between kinetic and potential energy (*16*). Although the precise mechanism of compensation in our study remains a mystery, an initial kinematic analysis revealed significant alterations in the biomechanics of walking that could be at the root of the reduction in metabolism. In particular, although there was no change in step frequency, the averaged vertical displacement of the hip during each step was 67.4 mm for the locked condition but only about 55.5 mm, or 11.9 mm less, for the unlocked condition (table S3). Further, there was an 11.8% (±SE = 1.67%, $n = 4$ participants, $P = 0.008$) reduction in the peak force exerted by the load back onto the person, as well as a change in phasing of this force with respect to the gait cycle (fig. S2). Because these factors will affect the magnitude and time course of forces, as well as the position of the center of mass, they will likely affect the amount of positive work that must be performed during the "double-support phase," a major determinant of the cost of walking (*17*–*21*).

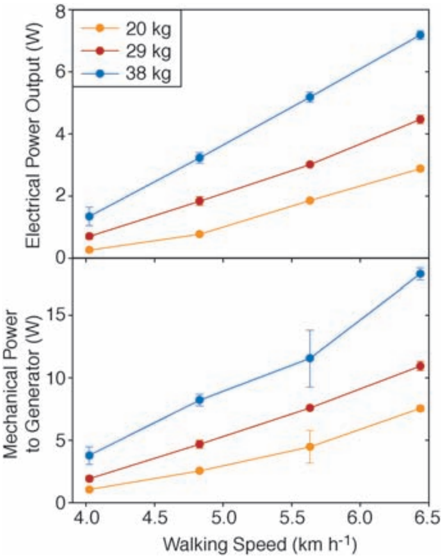

Fig. 4. The electrical power output and mechanical power input of the generator as a function of walking speed and load. This graph shows average values of four separate trials for each of 12 conditions for one person. The standard deviation bars are shown but are often smaller than the symbol.

Finally, despite the smaller than predicted Δmetabolic power input, individuals may have to carry extra food in order to power electricity generation. This weight, however, is negligible compared to the weight of batteries required to generate the same electrical energy. The specific energy of food (3.9×10^7 J kg^{-1}) (*22*) is about 100-fold greater than the specific energy of lithium batteries (4.1×10^5 J kg^{-1}) (*1*) and 35-fold greater than that of zinc-air batteries (1.1×10^6 J kg^{-1}). Given that the "metabolic efficiency of electricity generation" (electricity power output/Δmetabolic power input) is 19.5% (table S3), the extra food to be used for generating electricity would require about 20- and 6.8-fold less weight than lithium and zinc-air batteries, respectively (*23*). Hence, the longer the expedition, the greater the weight savings (*24*). Further, the ~12% reduction in peak force exerted on the body by a given load (fig. S2), as well as the potential for using some of the extracted mechanical energy directly for cooling the user (such as through forced air ventilation with a fan or pumping of a coolant) would provide additional ergonomic benefits to the user.

Throughout history, humans have solved many problems by inventing passive devices to enhance the movements made by their muscles (such as springy bamboo poles to carry loads or skis to move through the snow) (*25*, *26*). The suspended-load backpack is another passive device that may help solve a growing problem in the 21st century.

References and Notes

1. J. L. Gonzalez, A. Rubio, F. Moll, *Int. J. Soc. Mater. Eng. Resour.* **10**, 34 (2002).
2. J. Kymissis, C. Kendall, J. Paradiso, N. Gershenfeld, in *IEEE International Conference on Wearable Computing* (IEEE Computer Society Press, Los Alamitos, CA, 1998), pp. 132–139.

3. S. Georgi, www.batteriesdigest.com/id380.htm (accessed June 2005).
4. R. M. Alexander, *J. Exp. Biol.* **160**, 55 (1991).
5. G. A. Cavagna, N. C. Heglund, C. R. Taylor, *Am. J. Physiol.* **233**, R243 (1977).
6. J. Drake, *Wired* **9**, 90 (2001).
7. S. Stanford, R. Pelrine, R. Kornbluh, Q. Pei, in *Proceedings of the 13th International Symposium on Unmanned Untethered Submersible Technology* (Autonomous Undersea Systems Institute, Lee, NH, 2003).
8. T. Starner, J. Paradiso, in *Low Power Electronics Design* (CRC Press, Boca Raton, FL, 2004), p. 45–1.
9. G. A. Cavagna, M. Kaneko, *J. Physiol.* **268**, 647 (1977).
10. S. A. Gard, S. C. Miff, A. D. Kuo, *Hum. Mov. Sci.* **22**, 597 (2004).
11. Supporting material is available on *Science* Online.
12. Because it is a prototype, there has been no attempt to reduce the weight of the backpack—indeed, it is substantially "overdesigned." Further, the 5.6 kg includes the weight of six load cells and one 25-cm-long transducer, each with accompanying brackets and cables, as well as other components that will not be present on a typical pack. In future prototypes, we estimate that the weight will exceed that of a normal backpack by no more than 1 to 1.5 kg.
13. Under high-power conditions (5.6 km hour^{-1} with 20- and 29-kg loads and 4.8 km hour^{-1} with a 38-kg load), power generation on the incline was the same as on the flat. Under low-power conditions (4.8 km hour^{-1} with 20- and 28-kg loads), electricity generation on the incline was actually substantially greater than that on the flat (table S1).
14. R. Margaria, *Biomechanics and Energetics of Muscular Exercise* (Clarendon, Oxford, 1976).
15. R. A. Ferguson *et al.*, *J. Physiol.* **536**, 261 (2001).
16. G. A. Cavagna, P. A. Willems, M. A. Legramandi, N. C. Heglund, *J. Exp. Biol.* **205**, 3413 (2002).
17. A. Grabowski, C. T. Farley, R. Kram, *J. Appl. Physiol.* **98**, 579 (2005).
18. J. M. Donelan, R. Kram, A. D. Kuo, *J. Exp. Biol.* **205**, 3717 (2002).
19. J. M. Donelan, R. Kram, A. D. Kuo, *J. Biomech.* **35**, 117 (2002).
20. J. S. Gottschall, R. Kram, *J. Appl. Physiol.* **94**, 1766 (2003).
21. Because this savings in metabolic energy represents only 6% of the net energetic cost of walking with the backpack (492 W) (table S3) (*17*, *18*), accurate determinations of the position and movements of the center of mass, as well as the direction and magnitude of the ground reaction forces, are essential to discern the mechanism. This will require twin–force-platform single-leg measurements, as well as a complete kinematics and mechanical energy analysis (*19*, *20*). The energy analysis is made more complex because the position of the load with respect to the backpack frame and the amount of energy stored in the backpack springs vary during the gait cycle. Finally, electromyogram measurements are also important to test whether a change in effective muscle moment arms may have caused a change in the volume of activated muscle and hence a change in metabolic cost (*20*, *27*, *28*).
22. K. Schmidt-Nielsen, *Animal Physiology: Adaptation and Environment* (Cambridge Univ. Press, Cambridge, ed. 3, 1988).
23. This assumes that electronic devices are being powered in real time. If there were a power loss of 50% associated with storage (such as in batteries) and recovery of electrical energy, then these factors would be halved.
24. When not walking, the rack can be disengaged and the generator cranked by hand or by foot. Electrical powers of ~3 W are achievable by hand, and higher wattage can be achieved by using the leg to power it.
25. R. Kram, *J. Appl. Physiol.* **71**, 1119 (1991).
26. A. E. Minetti, *J. Exp. Biol.* **207**, 1265 (2004).
27. A. A. Biewener, C. T. Farley, T. J. Roberts, M. Temaner, *J. Appl. Physiol.* **97**, 2266 (2004).
28. T. M. Griffin, T. J. Roberts, R. Kram, *J. Appl. Physiol.* **95**, 172 (2003).
29. This work was supported by NIH grants AR46125 and AR38404. Some aspects of the project were supported by Office of Naval Research grant N000140310568 and a grant from the University of Pennsylvania Research Foundation. The authors thank Q. Zhang, H. Hofmann, W. Megill, and A. Dunham for helpful discussions; R. Sprague, E. Maxwell, R. Essner, L. Gazit, M. Yuhas, and J. Milligan for helping with the experimentation; and F. Letterio for machining the backpacks.

Supporting Online Material

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Figs. S1 and S2
Tables S1 to S4
References

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Accurate Multiplex Polony Sequencing of an Evolved Bacterial Genome

Jay Shendure,[1]*† Gregory J. Porreca,[1]*† Nikos B. Reppas,[1] Xiaoxia Lin,[1] John P. McCutcheon,[2,3] Abraham M. Rosenbaum,[1] Michael D. Wang,[1] Kun Zhang,[1] Robi D. Mitra,[2] George M. Church[1]

We describe a DNA sequencing technology in which a commonly available, inexpensive epifluorescence microscope is converted to rapid nonelectrophoretic DNA sequencing automation. We apply this technology to resequence an evolved strain of *Escherichia coli* at less than one error per million consensus bases. A cell-free, mate-paired library provided single DNA molecules that were amplified in parallel to 1-micrometer beads by emulsion polymerase chain reaction. Millions of beads were immobilized in a polyacrylamide gel and subjected to automated cycles of sequencing by ligation and four-color imaging. Cost per base was roughly one-ninth as much as that of conventional sequencing. Our protocols were implemented with off-the-shelf instrumentation and reagents.

The ubiquity and longevity of Sanger sequencing (*1*) are remarkable. Analogous to semiconductors, measures of cost and production have followed exponential trends (*2*). High-throughput centers generate data at a speed of 20 raw bases per instrument-second and a cost of $1.00 per raw kilobase. Nonetheless, optimizations of electrophoretic methods may be reaching their limits. Meeting the challenge of the $1000 human genome requires a paradigm shift in our underlying approach to the DNA polymer (*3*).

Cyclic array methods, an attractive class of alternative technologies, are "multiplex" in that they leverage a single reagent volume to enzymatically manipulate thousands to millions of immobilized DNA features in parallel. Reads are built up over successive cycles of imaging-based data acquisition. Beyond this common thread, these technologies diversify in a panoply of ways: single-molecule versus multimolecule features, ordered versus disordered arrays, sequencing biochemistry, scale of miniaturization, etc. (*3*). Innovative proof-of-concept experiments have been reported, but are generally limited in terms of throughput, feature density, and library complexity (*4–9*). A range of practical and technical hurdles separate these test systems from competing with conventional sequencing on genomic-scale applications.

Our approach to developing a more mature alternative was guided by several considerations. (i) An integrated sequencing pipeline includes library construction, template amplification, and DNA sequencing. We therefore sought compatible protocols that multiplexed each step to an equivalent order of magnitude. (ii) As more genomes are sequenced de novo, demand will likely shift toward genomic resequencing; e.g., to look at variation between individuals. For resequencing, consensus accuracy increases in importance relative to read length because a read need only be long enough to correctly position it on a reference genome. However, a consensus accuracy of 99.99%, i.e., the Bermuda standard, would still result in hundreds of errors in a microbial genome and hundreds of thousands of errors in a mammalian genome. To avoid unacceptable numbers of false-positives, a consensus error rate of 1×10^{-6} is a more reasonable standard for which to aim. (iii) We sought to develop sequencing chemistries compatible with conventional epifluorescence imaging. Diffraction-limited optics with charge-coupled device detection achieves an excellent balance because it not only provides submicrometer resolution and high sensitivity for rapid data acquisition, but is also inexpensive and easily implemented.

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[1] Department of Genetics, Harvard Medical School, Boston, MA 02115, USA. [2] Department of Genetics, [3] Howard Hughes Medical Institute, Washington University, St. Louis, MO 63110, USA.

*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: shendure@alumni.princeton.edu (J.S.), gregory_porreca@student.hms.harvard.edu (G.J.P.)