3. MacDonald, J. *et al.* Alternatives for landmine detection. Report No. RAND/MR-1608-OSTP (RAND Corp., Santa Monica, California, 2003).
4. Fischer, R., Burlage, R., DiBenedetto, J. & Maston, M. *Army AL&T.* July–August 2000, pp.10–12.
5. Jenkins, T.F. *et al.* Analysis of explosives-related signature chemicals in soil samples collected near buried landmines. Technical Report No. ERDC TR-00-5. (US Army Corps of Engineers, 2000).
6. Yagur-Kroll, S. *et al. Appl. Microbiol. Biotechnol.* **98**, 885–895 (2014).
7. Yagur-Kroll, S., Amiel, E., Rosen, R. & Belkin, S. *Appl. Microbiol. Biotechnol.* **99**, 7177–7188 (2015).
8. Palevsky, N., Shemer, B., Connolly, J.P.R. & Belkin, S. *Front. Microbiol.* **22**, 1490 (2016).
9. Kabessa, Y. *et al. Biosens. Bioelectron.* **49**, 394–398 (2013).
10. Kabessa, Y. *et al. Biosens. Bioelectron.* **79**, 784–788 (2016).
11. Nussinovitch, A. *Polymer Macro- And Micro-Gel Beads: Fundamentals And Applications* (Springer, New York; 2010).

Robotic crowd biology with Maholo LabDroids

To the Editor:

Concerns about the lack of reproducibility of experimental research[1,2], the numerous labor-intensive tasks required for high-throughput research, and the dangers (and costs) associated with experiments involving pathogens and harmful reagents led us to set up a Robotic Biology Consortium. We believe that the use of humanoid robots (which we term 'LabDroids') to carry out life science research experiments has the potential to minimize the above problems.

In 2009, the first robot scientist capable of devising hypotheses and then testing them was reported. By integrating automation technologies and data analysis pipelines, the robot, named Adam, was able to find new (and subsequently validated) information in yeast functional genomics experiments[3]. More recently, a robotic system was developed to enable precise and dexterous experiments with the model insect *Drosophila*[4]. Today, several startups, including Transcriptic (Menlo Park, CA, USA) and Emerald Cloud Lab (S. San Francisco, CA, USA), offer researchers remote access to laboratory automation systems to carry out experiments[5]. However, current laboratory automation systems are fixed assemblies of job-specific modules and can enable only a limited suite of experiments.

To establish a versatile laboratory automation system, we developed a high-performance LabDroid system named 'Maholo' (**Fig. 1a** and **Supplementary Video;** technical specifications to be published elsewhere). Maholo has one torso pivot and two arms, each of which has seven rotational axes and can manipulate laboratory tools and instruments without robot-specific modifications. The automation of various laboratory operations was first simulated using a computer-aided design system (**Fig. 1b**) and calibrated in a real environment. Maholo can carry out most regular tasks involving liquid handling in test tubes, Petri dishes, and microplate wells with the same pipettes and aspirators that human researchers and technicians use. The automated workflows for these tasks include a cell-harvesting process that requires delicate sample handling (**Fig. 1c**). In this process Maholo collects a cell culture dish from a CO_2 incubator and aspirates the culture medium before detaching the cells by trypsinization, then scrapes them free using a spatula with the correct pressure and speed, before collecting the cells in a tube. Unlike other laboratory automation systems, Maholo can reproduce human maneuvers without the assistance of action-specific jigs. Throughout cell culture harvesting, the left hand of Maholo serves as a jig to hold the culture dish, whereas the right hand performs several different tasks including dispensing, scraping, and transferring the cell suspension from dish to tube. This jig-free system enables greater flexibility in automating various laboratory protocols with a single robotic system. Force and vision sensors allow our LabDroid to manipulate other tools and devices, including a vortex mixer, sample mixers, tube rotors, incubators and refrigerators (**Fig. 1d**). For example, Maholo can open and shut a centrifuge door, press the front panel buttons and adjust the rotor angle with the aid of its vision system (**Fig. 1e**). Maholo can load tubes in a centrifuge in properly balanced positions and can salvage samples from the rotor, stopping at a random angle (**Fig. 1e**).

In any experiment that involves manual handling of reagents, it is inevitable that data variation will arise owing to human error. This variability could be minimized by the consistent movements, operation timings, and spatial trajectories of a LabDroid. One could argue that non-humanoid automation systems, such as liquid handling robots that can manipulate microtiter plates, could outperform LabDroids in precision and scalability for specific tasks. However, it is more challenging to automate complex workflows by combining such isolated job-specific automation systems, each of which is designed for human manipulation with minimal hardware and software engineering. Numerous tools in various combinations are used in the laboratory daily. Enormous efforts have already been devoted to optimizing these tools for human use. The cost of developing an integrated laboratory automation system with compatible modules to replace all of the experiments carried out in a typical laboratory would be prohibitively high. Instead, we propose that LabDroids, which can manipulate existing laboratory instruments, could form the basis of a versatile, scalable, and sustainable laboratory automation system that many laboratories might adopt.

The potential of LabDroids underpins our vision of robotic crowd biology, in which a crowd of LabDroids and an assortment of instruments in a large laboratory space are operated remotely online (**Fig. 2a**). LabDroids could be scaled to provide a versatile system comprising a team of droids that carry out

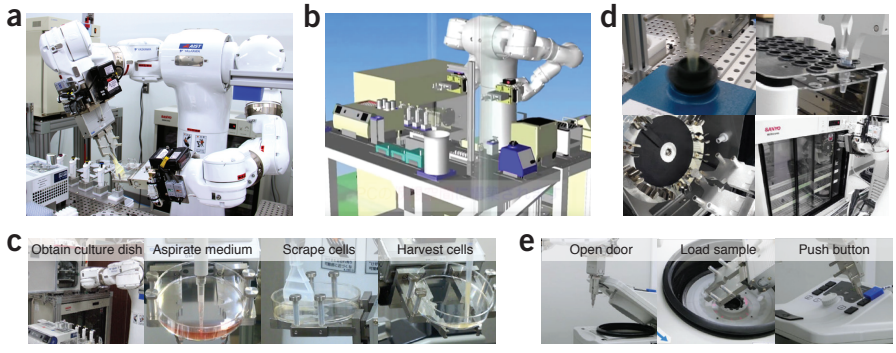

Figure 1 LabDroid system. (**a**) Maholo system. (**b**) Computer-aided design software system defines Maholo's job operations. (**c**) Demonstration of automated cell-harvesting process. Cell culture dish is obtained from a CO_2 incubator; supernatant is aspirated; and upon trypsinization, cells are collected using a spatula and a pipette. (**d**) Examples of tools Maholo manipulates: (top left) vortex mixer, (top right) sample mixer, (bottom left) rotor, (bottom right) refrigerator. (**e**) Centrifugation process.

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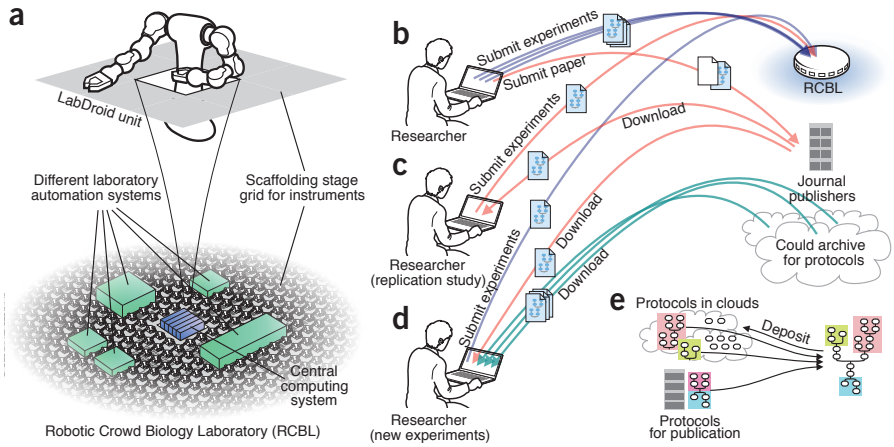

Figure 2 Robotic crowd biology concept. (**a**) RCBL, a large laboratory automation field with a number of LabDroids manipulating a wide range of laboratory tools, instruments, and job-specific automation systems. Each LabDroid is allocated a different set of instruments and a central computing system dynamically schedules the cooperation of multiple LabDroids. (**b**) Researcher designs and submits protocols online to an RCBL. The same protocols can be provided to the public in paper publications. (**c**) Published experiments can be replicated by downloading the protocols and resubmitting them to the same or another RCBL. (**d**) New experiments can be efficiently constructed by rewiring existing protocol resources. (**e**) Sustainable model for reusing and expanding protocols published by journals.

job-specific laboratory automation systems combined with human-usable tools. In such a robotic crowd (or cloud) biology laboratory (RCBL), experimental protocols are sent online and samples are shipped from all over the world (**Fig. 2b**). Reagents and samples are barcoded and linked to the corresponding process in the protocols. Barcode scanning and automated internal delivery systems allocate reagents and samples around LabDroids that operate experiments. A timeline of each experimental step is extracted automatically from the submitted protocol, with information for materials and instruments. A single LabDroid does not perform a whole experiment by itself, but a team of LabDroids can perform multiple experiments simultaneously based on an 'agent crowd operation'. For each sub-process in the different experiments in the queue, the central computing system dynamically assigns available LabDroids that are close to optimal instruments and thereby maximizes the production of the whole RCBL.

The development of an RCBL could provide a new way of doing life science research. All materials and methods implemented in an RCBL would be complete and robust. The availability of crowdsourced protocols that are continually recorded, tested, and validated by robotic systems that automatically report each experiment might alleviate the reproducibility crisis by having protocols described in a standard notation that could be attached to manuscripts submitted to journal publishers, and in turn serve as primary resources for replication and modification studies (**Fig. 2b**,**c**). Using protocol editing software, new protocols could be efficiently developed by modifying different layers of existing job and workflow modules stored in online protocol archives, in which the number of reutilizations for each module can be traced (**Fig. 2d**,**e**), as an alternative to evaluating researcher contributions. Furthermore, researchers could outsource large-scale experiments to an RCBL by applying a range of modifications to a pilot experiment carried out in their own laboratory. Similarly, high-biosafety-level studies could be readily executed by LabDroids.

Using an RCBL, instruments could be shared, and waiting time and space surplus could be minimized by the central computing system's dynamic optimization of resource assignments. Plans for installing, replacing, and leasing equipment could be computed from the experiment history and trend information. The RCBL actualizes 'lab-less' research; once process automations accumulate with their reutilization and reliability information to a certain threshold, precision experiments can be designed and executed without testing the performance of each robotic operation. This might conceivably provide access to life science research by a broad community of people, for example, HIV research by high-school scientists.

To scale the current single LabDroid-based system up to an RCBL, a standard framework needs to be developed for describing experimental protocols, operating system assemblies, and recording results. Currently, Maholo's proprietary software system and application program interface enables only Maholo to perform experimental tasks. Although robotic operation frameworks are also provided by several services, including Transcriptic, Emerald Cloud Lab, Aquarium (a product of Eric Klaven's group at the University of Washington, Seattle) and Synthace's (London) Antha, no practical framework has been proposed to transfer protocols among different laboratory automation systems or to freely integrate different tools and automation systems to automate complex experimental operations. We propose that a scalable laboratory automation should be split into two layers: first, a standard semantic layer, or process ontology layer, in which experimental workflows are described by connecting various job processes ('process description'); and second, a translation layer, in which each job process described in the standard semantics is compiled into robotic operations for a given operation environment ('process-to-operation mapping'). The first layer could be actualized from an open science community by harnessing previous efforts for process ontology for laboratory experiments[6–9]. The second layer would require the manufacturing side to prepare its process-to-operation mapping for different job processes defined using the standard syntax.

At present, laboratory automation processes generally suffer from the 'hard coding' of systems and manual adjustments to sensitive environmental differences, which are usually not well documented. However, for LabDroids that have sensing systems and form an RCBL, robotic behaviors in a specified environment could be fed back to the central computing system and automatically optimized with the support of artificial intelligence. This would allow the ideal automated process-to-operation mapping or 'real world programming of experiments' (much like compiling a program script in a particular computational hardware environment).

Phase I of the Robotic Biology Consortium is to build a few small-scale RCBLs by early 2020. Each RCBL will be composed of multiple LabDroids, laboratory automation systems, and human-usable experimental tools and equipment. We plan to demonstrate fully remote operation of complex experiments in genomics, proteomics, and high-content cell screening, and to showcase the reproducibility of the experiments exchanged between different RCBLs.

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Although substantial challenges remain, such as the establishment of widely agreed upon standard semantics, massively parallel operation of robotic crowds and instruments, and the implementation of artificial intelligence, robotic crowd biology using the LabDroid-centered system has the potential to scale current life science and laboratory automation in a robust and reproducible way.

Editor's note: This article has been peer-reviewed.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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AUTHOR CONTRIBUTIONS
N.Y. formulated the grand design of robotic crowd biology, prepared the figures, and wrote the manuscript. T.N. led the development of Maholo with the Robotic Biology Consortium and wrote the manuscript.

COMPETING FINANCIAL INTERESTS
The authors declare competing financial interests: details are available in the online version of the paper.

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1. McNutt, M. *Science* **346**, 679 (2014).
2. Nuzzo, R. *Nature* **526**, 182–185 (2015).
3. King, R.D. *et al. Science* **324**, 85–89 (2009).
4. Savall, J., Ho, E.T., Huang, C., Maxey, J.R. & Schnitzer, M.J. *Nat. Methods* **12**, 657–660 (2015).
5. Check Hayden, E. *Nature* **516**, 131–132 (2014).
6. Smith, B. *et al. Nat. Biotechnol.* **25**, 1251–1255 (2007).
7. Soldatova, L.N., Clare, A., Sparkes, A. & King, R.D. *Bioinformatics* **22**, e464–e471 (2006).
8. Soldatova, L.N. *et al. BMC Bioinformatics* **15** Suppl 14, S5 (2014).
9. Vita, R., Overton, J.A., Greenbaum, J.A., Sette, A. & Peters, B. *J. Biomed. Semantics* **4** Suppl 1, S6 (2013).

With all due respect to Maholo, lab automation isn't anthropomorphic

To the Editor:
Biosciences journals often require rigorous statistical evidence for the data presented because a substantial proportion of the biosciences literature is not reproducible[1]. In this issue, Yachie *et al.*[2] propose that LabDroids could form part of a robotic infrastructure that might contribute to improved reproducibility. However, we argue that reproducible research can be enabled by existing (or new) automation technologies present in both individual research groups and centralized DNA foundries that can be accessed using cloud-based applications.

Most bioscience experiments move small amounts of liquid from one place to another in order to set up experiments and measure effects. Scientists use tools, such as adjustable micropipettes, first launched by Eppendorf (Hamburg, Germany) in 1961, to move liquids in the microliter range. Based on similar principles, automated technologies were developed to enable high-throughput processing. These technologies were mainly developed to screen large chemical libraries for drug leads in the pharmaceutical industry. The Beckman Coulter (Brea, CA, USA; then SmithKline Coulter) Biomek 1,000-tip-based liquid handler system was introduced in 1986,

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