DNA construction software saves time, resources and money

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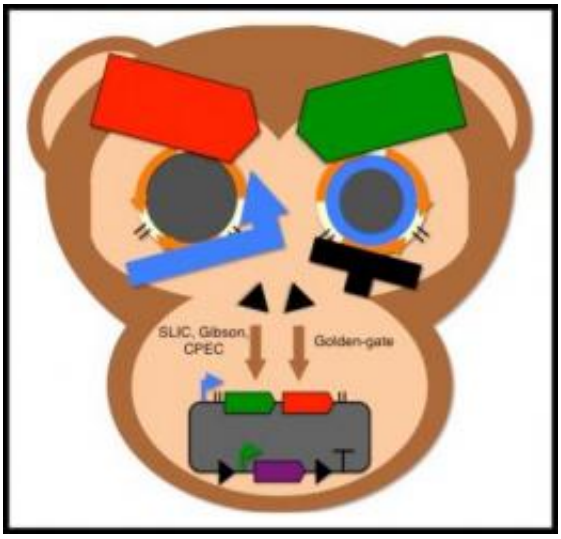


The j5 software provides a single design for the SLIC, Gibson, CPEC and Golden Gate DNA assembly strategies and determines which would be most advantageous for a given construction project. Credit: Nathan Hillson

DNA construction, also known as DNA cloning or recombinant DNA technology - among a host of other terms - is one of the principal tools of modern biotechnology, used for a wide variety of purposes, including genetic studies, medical research, and the development of advanced biofuels. A number of software programs make the process faster and more efficient, but Nathan Hillson, a biochemist at the U.S. Department of Energy (DOE)'s Joint BioEnergy Institute (JBEI), with an eye on the economics of scientific discovery, has developed the only DNA

construction software that also identifies which strategy would be the most cost-effective. This unique software program goes by the unassuming name of j5.

"Our j5 is the only software package today that both standardizes and cost-optimizes the DNA construction process," says Hillson, who directs JBEI's Synthetic Biology program and also holds an appointment with the Lawrence Berkeley National Laboratory (Berkeley Lab)'s Physical Biosciences Division. "Through the design of short DNA sequences that can be used to join longer sequences together in recombinant DNA assemblies, the j5 software improves the accuracy, scalability, and cost-effectiveness of DNA construction."

DNA construction is the process by which multiple genes or fragments of DNA sequences are physically assembled together. Such constructs are valuable for developing new medical treatments and for engineering microbes to efficiently carry out a specific task, such as converting cellulosic biomass into clean, green, renewable transportation fuels.

DNA construction incorporates DNA sequence fragments - often referred to as "parts" - from a variety of organisms into a self-replicating genetic element, such as a bacterial plasmid, that will propagate the assembled parts in a host cell. Traditionally, this has been accomplished through the use of a panoply of restriction enzymes for splicing desired DNA sequence fragments, and ligation enzymes for bonding the fragments to plasmid cloning sites.

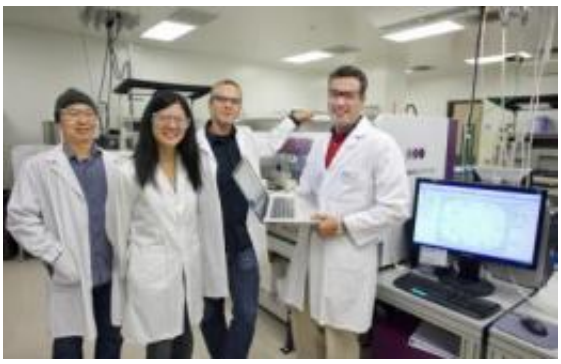
"As the size and number of parts to be incorporated into the plasmid increases, traditional construction of recombinant DNA assemblies becomes ever more difficult," says Hillson. "The process must often be repeated from scratch for alternate combinations of parts, and every time you clone a different gene or fragment, you might have to use a different pair of restriction sites. This has been a labor-intensive and

time-consuming process."

With modern DNA construction techniques, Hillson says, a small number of enzymes can be used over and over again, independent of the DNA sequence fragments being assembled, and thereby enabling automation with robotic platforms. However, designing protocols for these modern DNA construction approaches can be as labor-intensive, time-consuming and error-prone as the traditional approach. Furthermore, it is now increasingly important to consider outsourcing portions of DNA construction - to companies that chemically synthesize long sequences of DNA – as a cost-effective alternative. To address these considerations Hillson created the j5 software package.

"The j5 software package is a Web-based computer application that automatically designs and optimizes state-of-the-art DNA construction protocols," Hillson says. "Within minutes it can determine the optimal flanking sequences that should be attached to each DNA part to produce the desired recombinant DNA at the least expense, in a manner that is executable by hand or robotics."

As a result, researchers can direct their resources to investigating their primary interests, rather than preparing the DNA that is merely a tool in their experiments.



(From left) Timothy Ham, Joanna Chen, Rafael Rosengarten and Nathan Hillson have developed j5, the only DNA construction software that not only makes the process faster and more efficient but also identifies which construction strategy would be the most cost-effective. Credit: Photo by Roy Kaltschmidt, Berkeley Lab

"At JBEI, we want researchers spending their time designing their DNA constructs and assaying their function," Hillson says. "We don't want them to waste their time building these things in the lab, so we're trying to go after ways of taking that burden off them."

In addition to identifying the most cost-effective strategies for DNA cloning, j5 also makes it possible to construct combinatorial libraries – collections of hundreds to millions of related DNA assemblies, each with a different combination of genes or parts that perform similar functions in different organisms. Combinatorial libraries enable scientists to select the most effective genetic combination for achieving a desired result, e.g., the most efficient production of a biofuel or medication in a given host. No other automated DNA cloning software does this on the same scale and as fast and effectively as j5.

"Combinatorial libraries can be screened to identify the gene combination that, when transferred into a desirable host organism, results in the most productive enzyme pathway," says Hillson. "The j5 software is the only program that enables the combinatorial design of scarless DNA construction methods."

Traditional DNA construction methods result in scars - uncontrolled portions of the DNA sequence - at DNA fragment junctions that can adversely impact function. Says Hillson,

"The gold standard for combinatorial libraries is the ability to control the DNA sequence at every single base pair and this is what j5 allows you to do."

The j5 software package features a graphical interface that enables users to design a DNA construct or combinatorial libraries through the arrangement of individual part icons that abstractly represent underlying DNA sequences. Outputs are in the form of user-friendly spreadsheets that detail the resulting designed experimental protocols, providing instructions that can either be followed by a person in the laboratory or fed directly into a robotic platform for a machine to carry out.

"Our j5 software is already allowing a growing number of scientists to save financial resources and months of work that was previously devoted to constructing recombinant DNA, and has now been redirected to other fruitful aspects of their work," Hillson says. Currently, over 110 institutions worldwide are registered users of j5.

More information: j5.jbei.org/

Provided by Lawrence Berkeley National Laboratory