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Structural basis for transcriptional regulation by the cell division regulator MraZ in *Mycoplasma genitalium*

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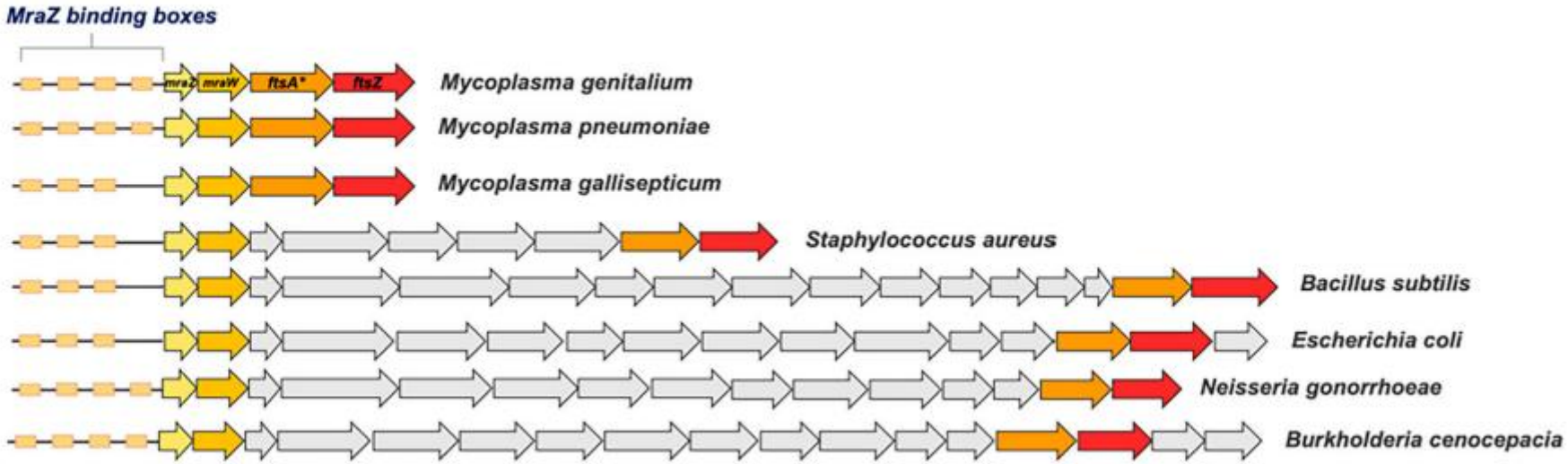
Cell division is a central process in all living organisms and requires the coordinated action of many proteins and regulatory elements. In most bacteria, the division and cell wall (dcw) gene cluster is regulated by the first gene of the dcw operon, mraZ, a highly conserved DNA-binding transcriptional regulator. Here

- A research team led by Universitat Autònoma de Barcelona (UAB) scientist David Reverter has identified the molecular mechanism that regulates bacterial cell division. The discovery reveals how the MraZ protein binds to the dcw gene cluster to control this process. The findings were published in *Nature Communications*.

Cell division is essential for all living organisms and depends on the coordinated activity of many proteins and regulatory components. In most bacteria, the instructions for this process are organized within a group of genes known as the dcw operon. This cluster contains the genetic information needed to produce proteins responsible for both cell division and the construction of the bacterial cell wall.

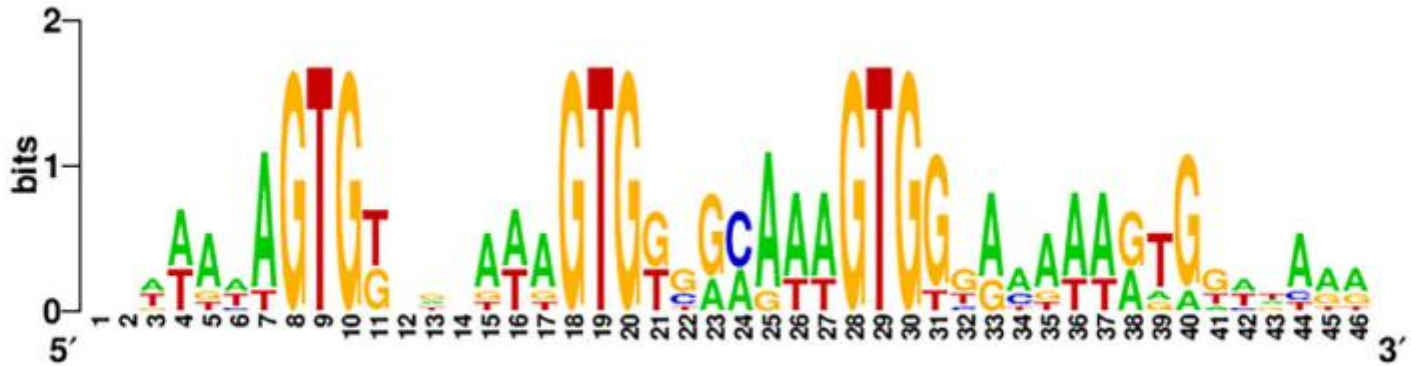
a



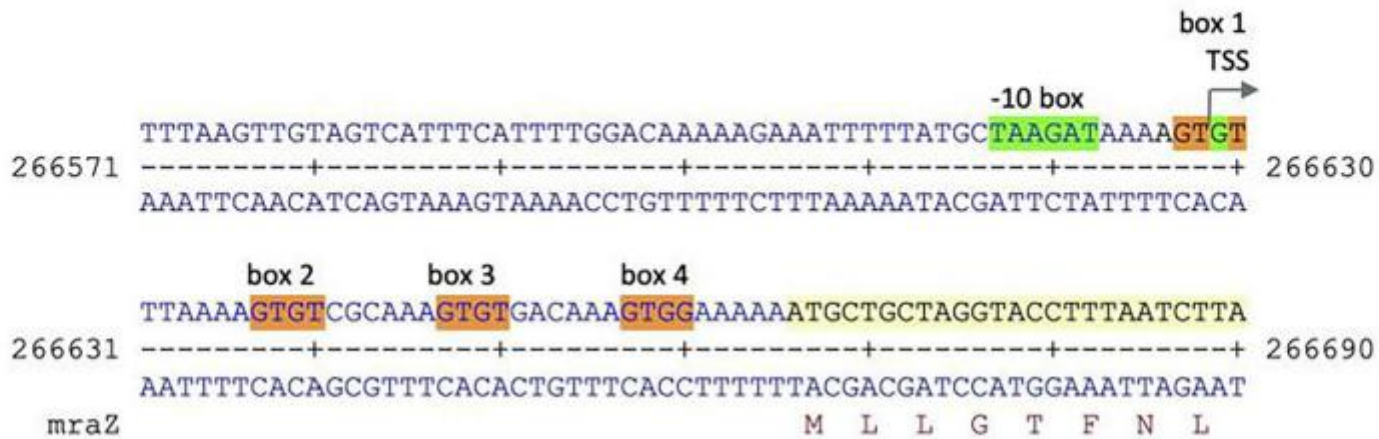
b

Mycoplasma genitalium	GATAAAA**GTGT**TTAAAA**GTGT**CGCAAA**GTGT**GACAAA**GTGG**AAAAA
Mycoplasma pneumoniae	ATATAAA**GTGT**TTTAAA**GTGT**CACAAA**GTGG**CATAAA**GTGG**TAAAA
Mycoplasma gallisepticum	TTGAAAA**GTGT**TAAAAA**GTGT**GACAAA**GTGG**GAAAAAATGATTTAA
Staphylococcus aureus	ATAAATA**GTGG**TGGATA**GTGG**GGAGAT**GTGG**TAAATTATATATAAG
Bacillus subtilis	TGAAGTT**GTGG**AGCGAA**GTGG**TGAATA**GTGG**TGAGTTAAGGAGAGA
Escherichia coli	CCTTTCA**GTGG**GAAATT**GTGG**GGCAAA**GTGG**GAATAAGGGGTGAGG
Neisseria gonorrhoeae	TCTTATA**GTGT**CGATTG**GTGG**GGAATT**GTGG**GGCAAA**GTGT**CTCTT
Burkholderia cenocepacia	CTCTAAA**GTGG**GAGACA**GTGT**GAGAAA**GTGT**ATTTTT**GTGT**GATTT

Operon:
A unit of DNA in bacteria and some other organisms consisting of a group of genes controlled by a single promoter and regulated together.


bits
2
1
0
5′
3′

C

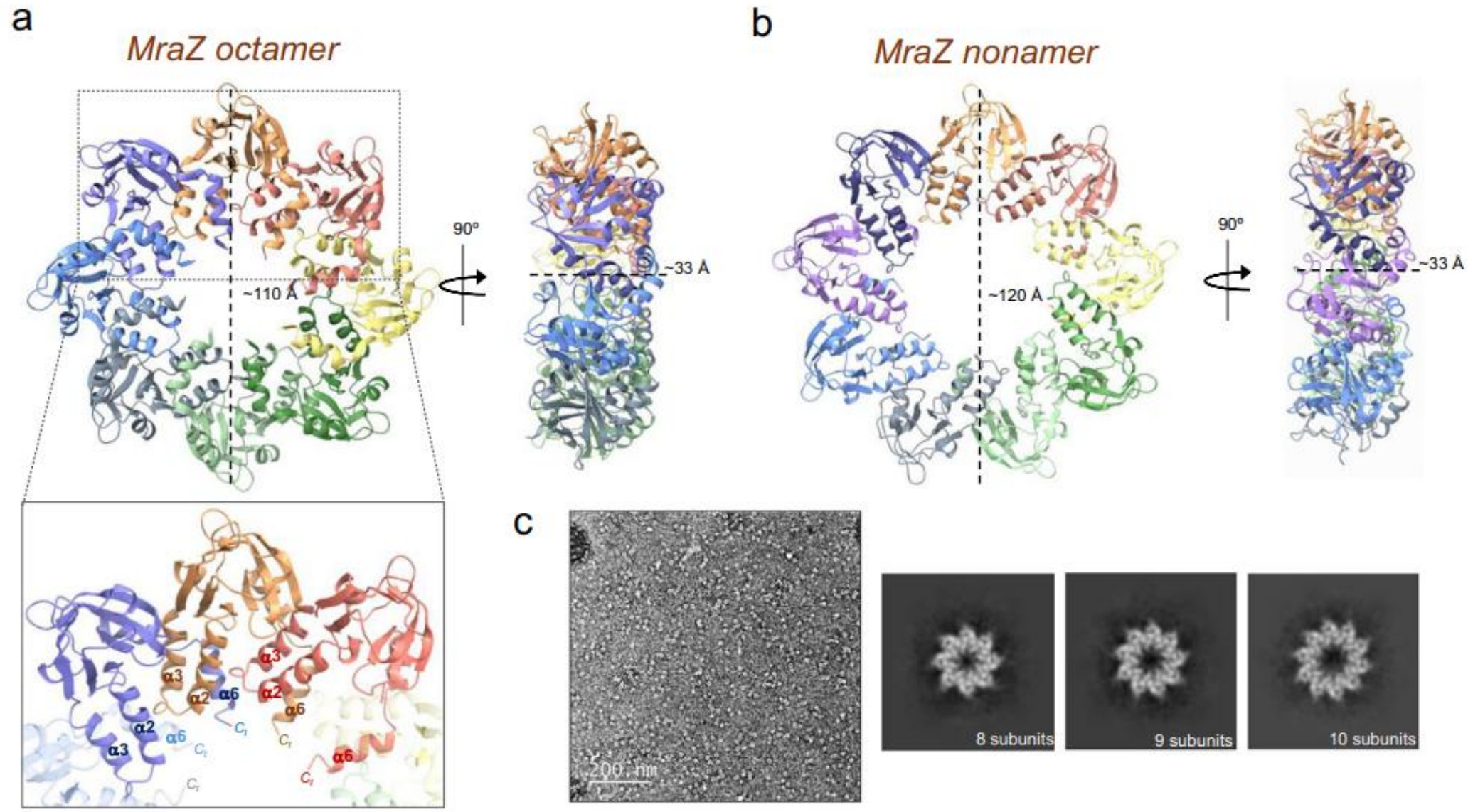

box 1
TSS
-10 box
TTTAAGTTGTAGTCATTTCATTTTGGACAAAAAGAAATTTTTATGCTAAGATAAAAGTGT
266571 266630
AAATTCAACATCAGTAAAGTAAAACCTGTTTTTCTTTAAAAATACGATTCTATTTTCACA
box 2
box 3
box 4
TTAAAAGTGTCGCAAAGTGTGACAAAGTGGAAAAAATGCTGCTAGGTACCTTTAATCTTA
266631 266690
AATTTTCACAGCGTTTCACACTGTTTCACCTTTTTTACGACGATCCATGGAAATTAGAAT
mraZ
M L L G T F N L

The genes in this cluster are turned on by proteins known as transcription factors. These proteins attach to a specific section of DNA called the promoter, which marks where transcription begins. This starting point appears just before the first codon (the basic unit of gene information) that signals the beginning of the protein sequence.

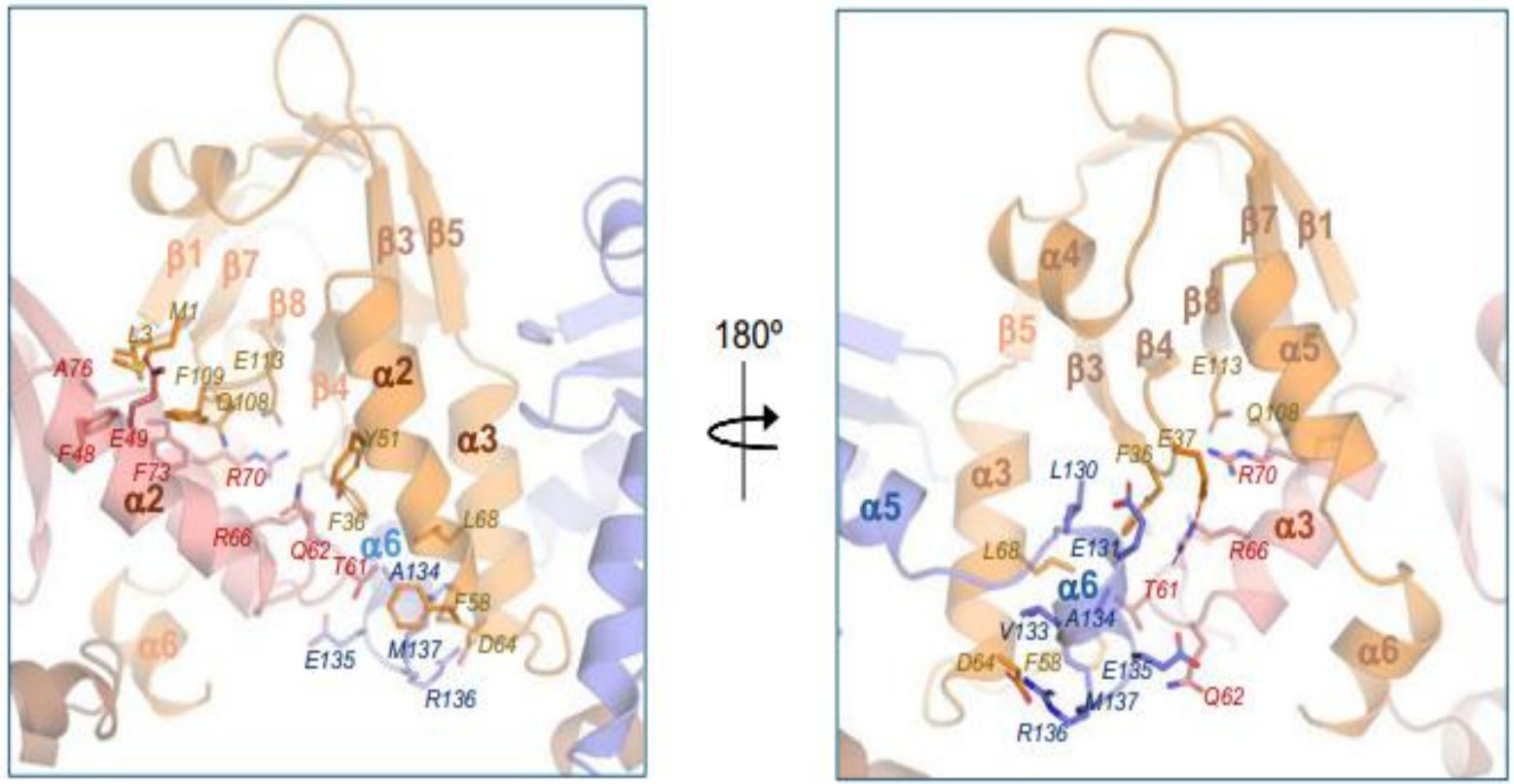
Imaging the Molecular Mechanism of Bacterial Division

The UAB research group, led by David Reverter, full professor in the Department of Biochemistry and Molecular Biology and researcher at the Institute of Biotechnology and Biomedicine of the UAB (IBB-UAB), uncovered the detailed mechanism behind this regulation. The team used advanced structural biology methods including X-ray crystallography and cryo-electron microscopy.

These techniques allowed the scientists to determine how the MraZ transcription factor attaches to the promoter of the dcw operon in the bacterium *Mycoplasma genitalium*. This microorganism is frequently used in laboratory studies because it possesses an extremely small genome.

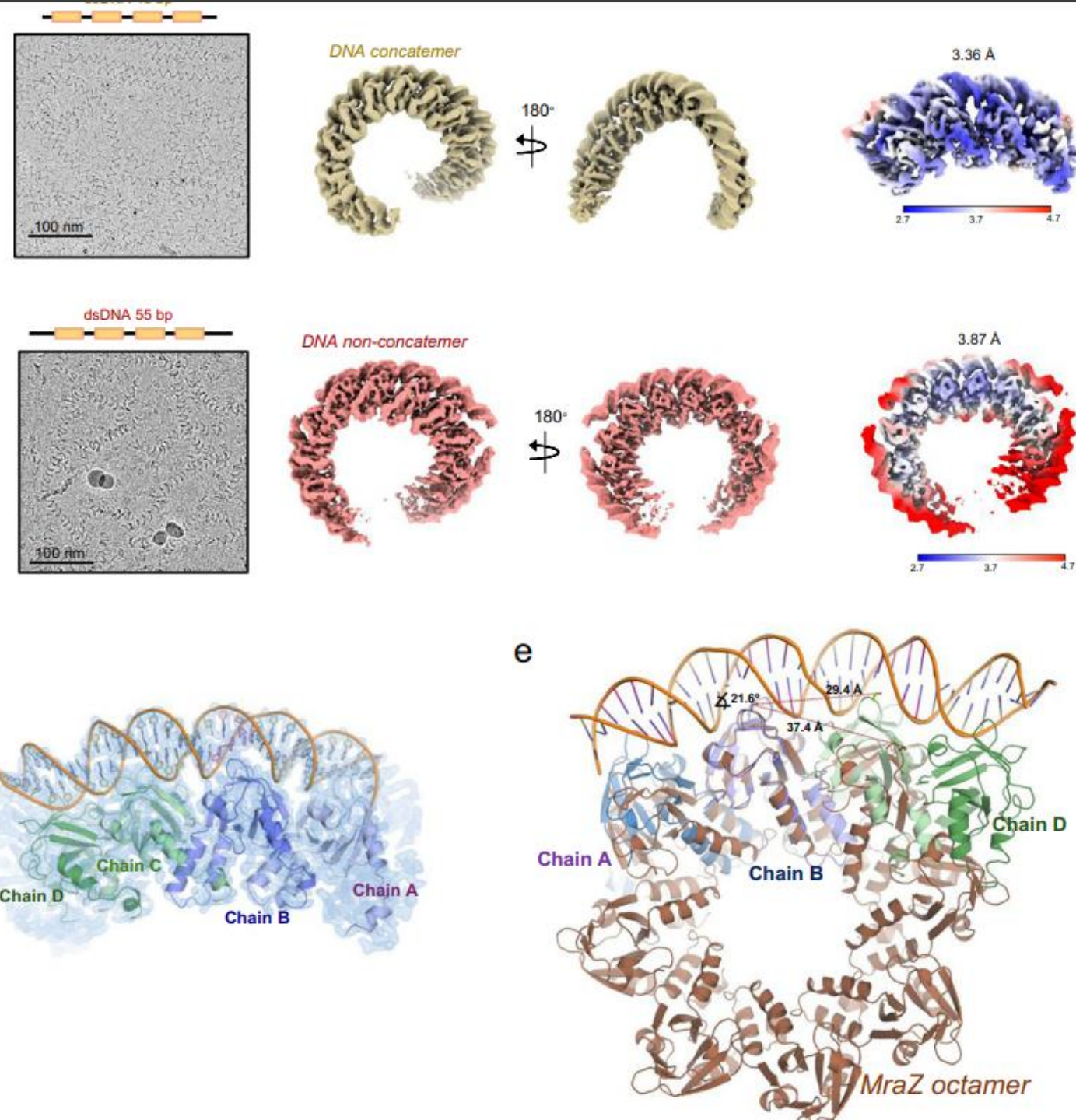

a
MraZ octamer
~110 Å
90°
~33 Å
α3
α2
α6
b
MraZ nonamer
~120 Å
90°
~33 Å
c
200 nm
8 subunits
9 subunits
10 subunits

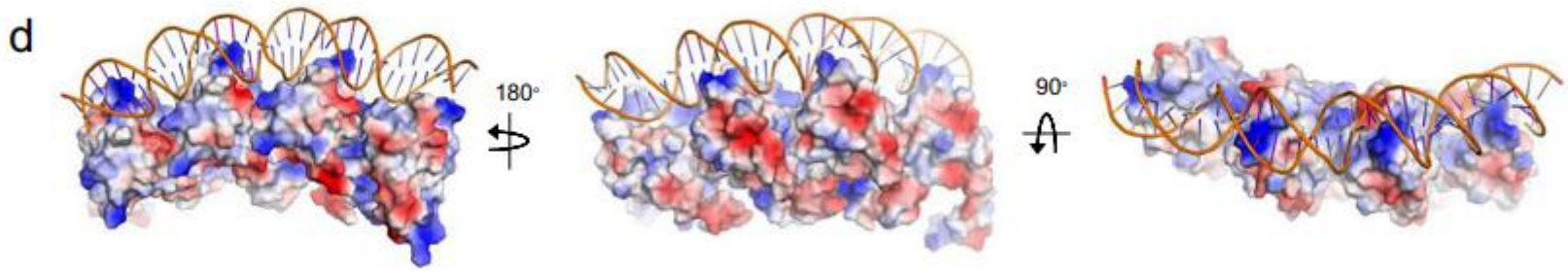
d

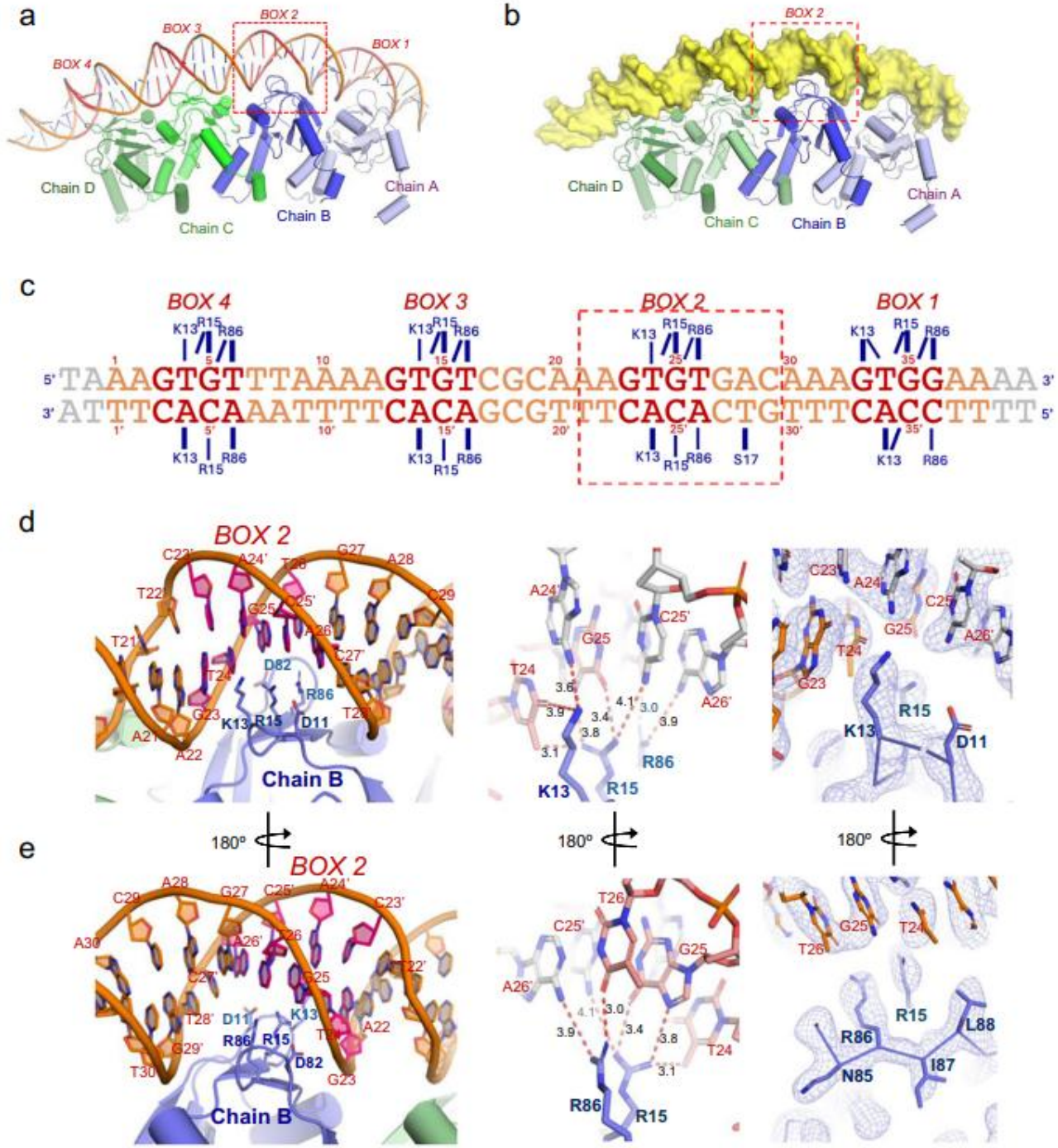

β1
β7
β3
β5
β8
M1
L3
A76
F109
E113
β4
α2
Q108
E49
Y51
α3
F48
F73
R70
α2
F36
L68
R66
Q62
α6
T61
A134
F58
α6
D64
E135
M137
R136
180°
α4
β7
β1
β8
β5
β4
β3
E113
α5
Q108
E37
F36
α3
L130
R70
α5
α3
L68
E131
R66
α6
T61
V133
A134
D64
F58
E135
Q62
M137
α6
R136

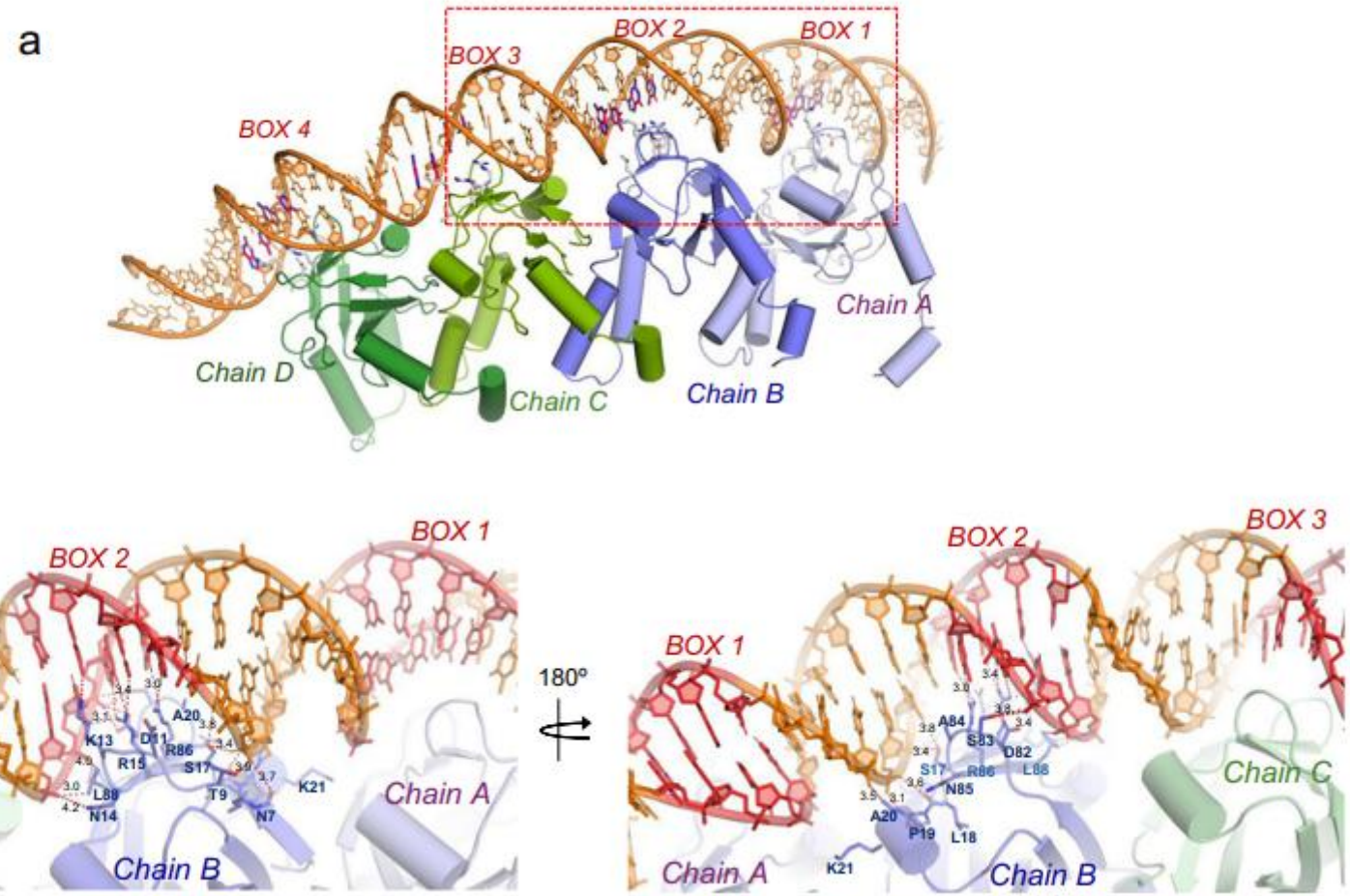
The promoter region of the dcw operon contains four repeated segments, or "boxes," each composed of six nucleotides. These repeated DNA sequences play a key role in regulating transcription.

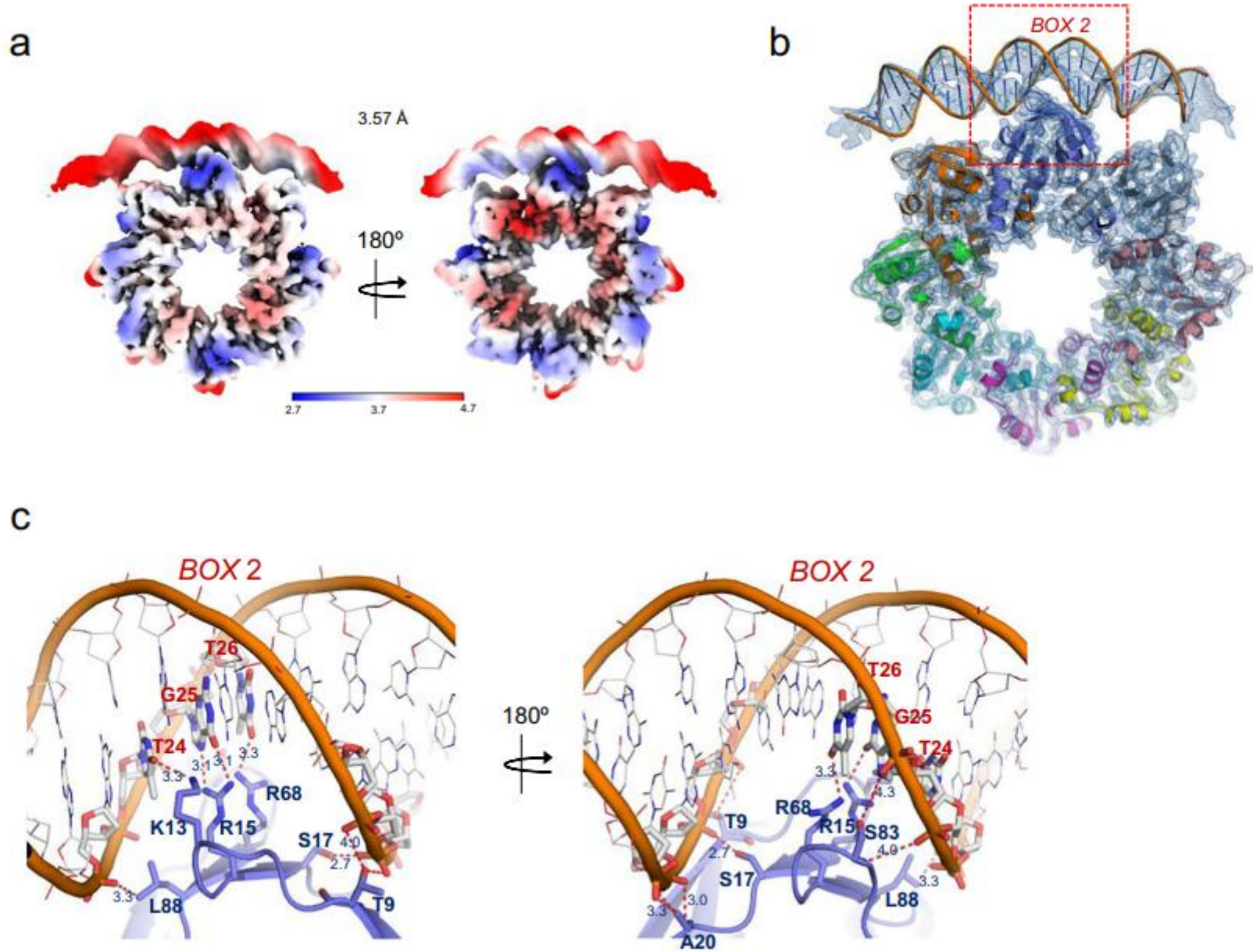
By examining the system with cryo-electron microscopy, the researchers were able to observe the interaction between the MraZ protein and the DNA bases of these four repeated boxes at nearly atomic resolution. Their observations showed that MraZ must undergo a structural change in order to bind successfully to the operon.

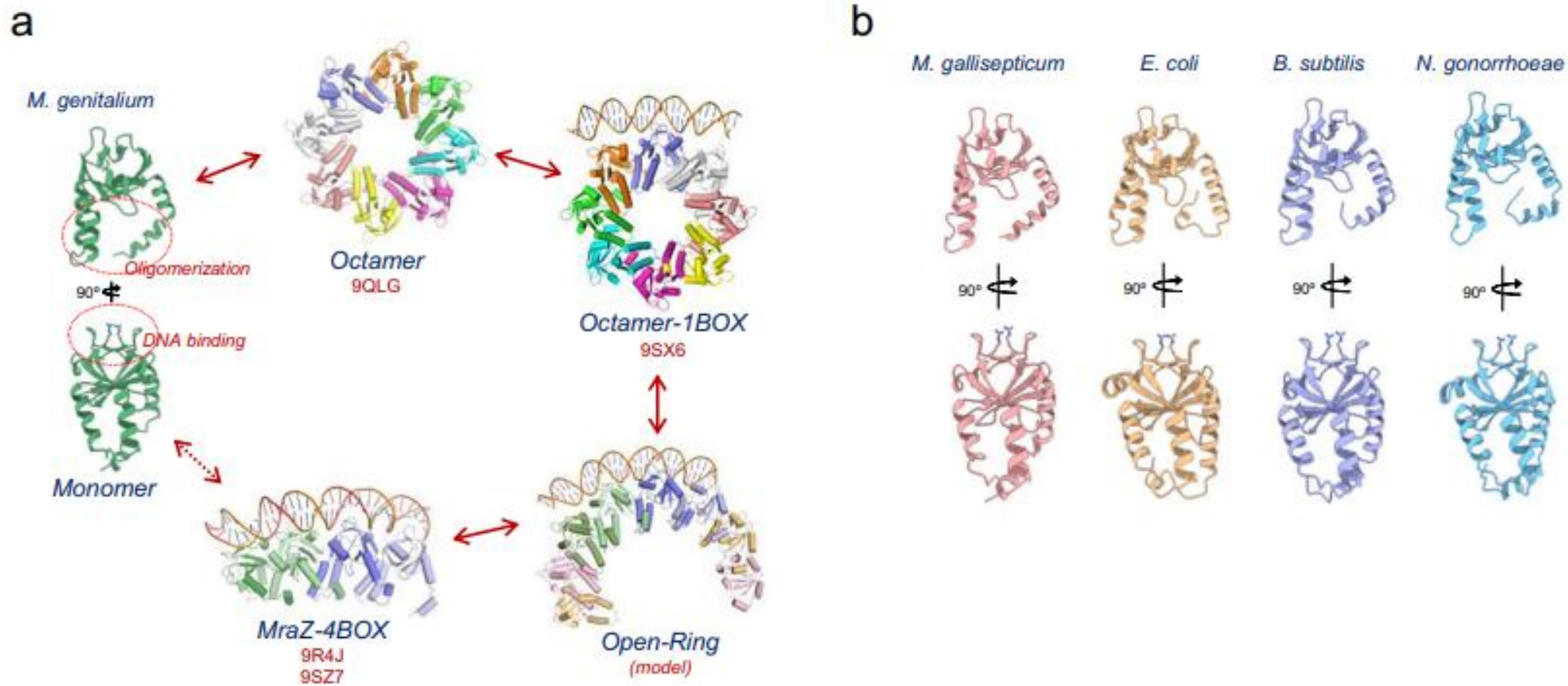

100 nm
DNA concatemer
180°
3.36 Å
2.7
3.7
4.7
b
dsDNA 55 bp
100 nm
DNA non-concatemer
180°
3.87 Å
2.7
3.7
4.7
c
Chain C
Chain D
Chain B
Chain A
e
21.6°
29.4 Å
37.4 Å
Chain A
Chain B
Chain D
MraZ octamer


d
180°
90°


a
BOX 4
BOX 3
BOX 2
BOX 1
Chain D
Chain C
Chain B
Chain A
b
BOX 2
Chain D
Chain C
Chain B
Chain A
c
BOX 4
BOX 3
BOX 2
BOX 1
5' TAAAGTGTTTAAAAGTGTCGCAAAGTGTGACAAAGTGGAAAA 3'
3' ATTTCACAAATTTTCACAGCGTTTCACACTGTTTCACCTTTT 5'
K13
R15
R86
S17
d
BOX 2
Chain B
e
180°
BOX 2
Chain B
R15
R86
L88
N85
I87


a
BOX 3
BOX 2
BOX 1
BOX 4
Chain A
Chain D
Chain C
Chain B
b
BOX 3
BOX 2
BOX 1
Chain C
Chain B
Chain A
180°
BOX 1
BOX 2
BOX 3
Chain A
Chain B
Chain C


a
3.57 Å
180°
2.7
3.7
4.7
b
BOX 2
c
BOX 2
T26
G25
T24
R68
K13
R15
S17
T9
L88
180°
BOX 2
T26
G25
T24
T9
R68
R15
S83
S17
L88
A20


a
M. genitalium
Oligomerization
90°
DNA binding
Monomer
Octamer
9QLG
Octamer-1BOX
9SX6
MraZ-4BOX
9R4J
9SZ7
Open-Ring
(model)
b
M. gallisepticum
E. coli
B. subtilis
N. gonorrhoeae
90°
90°
90°
90°

to regulate cell division we see how the donut breaks and deforms in such a way that four of the sub-units can join the four boxes of the promoter

A Major Advance in Understanding Bacterial Cell Division

Directly visualizing how MraZ interacts with the promoter DNA that initiates cell division represents a significant breakthrough. Until now, researchers studying this system relied largely on biochemical experiments and computer modeling to infer how the mechanism worked.

the regulatory system identified in this study is likely widespread among bacteria. "is universal to most bacteria, since all MraZ proteins are very similar, have the same octamer structure, and the DNA sequences of the promoters of the operons that regulate cell division are also similar,