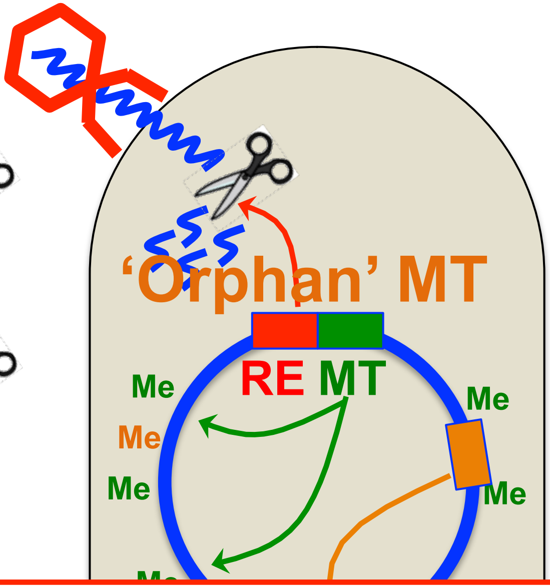
Bacterial epigenomics

Genome technologies Workshop
03/24/15
Matthew Blow

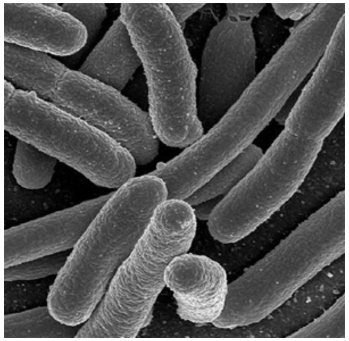
Why Study DNA modification in Bacteria?

1. Restriction systems

Methylase (MT) protects host DNA



2. Regulation



Genome regulation

G$\overset{Me}{A}$TC in *E.Coli and other γ-proteobacteria*

Cell cycle regulation

in

acteria

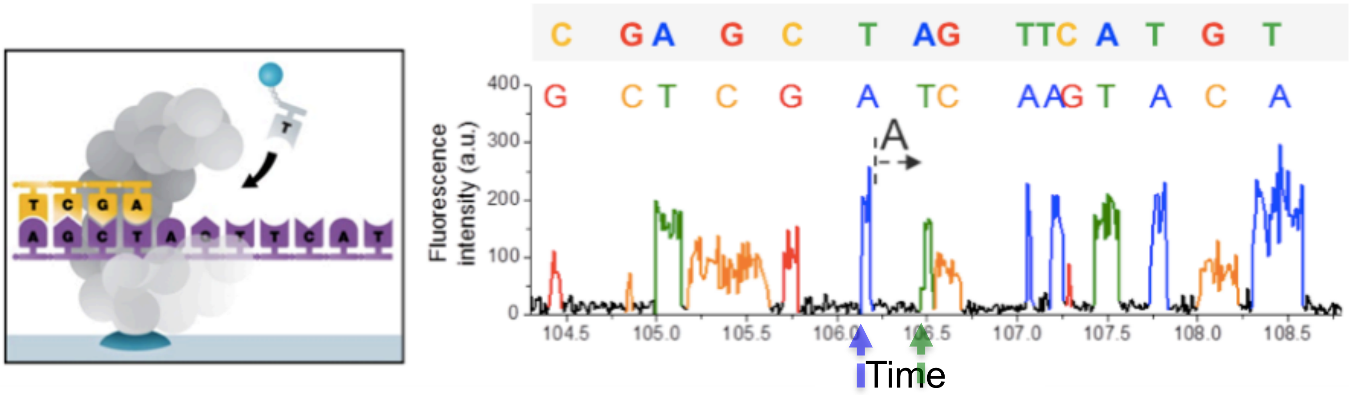
s?

Problem:

Lack of tools for studying Prokaryotic methylation types (6mA, 4mC)

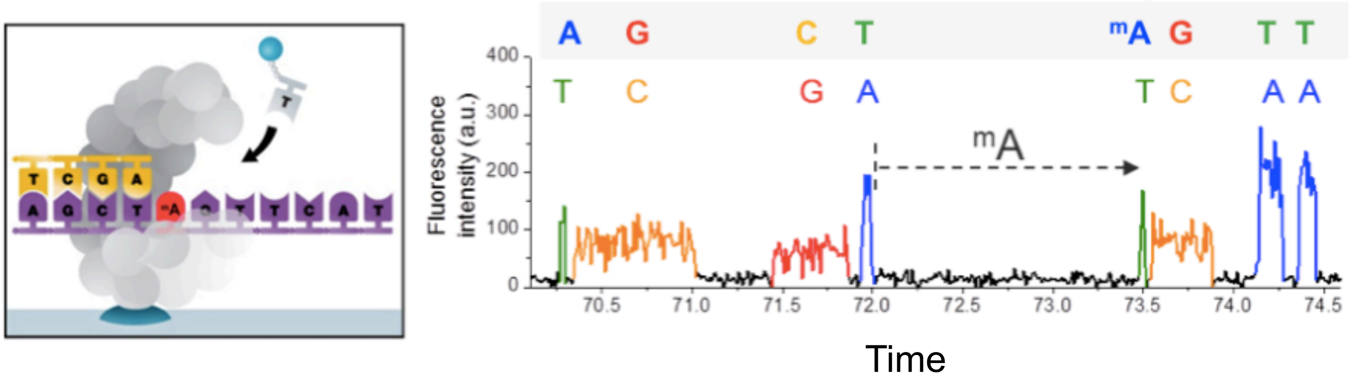
Prokaryotic DNA methylation can be directly detected by PacBio sequencing

Unmodified DNA template

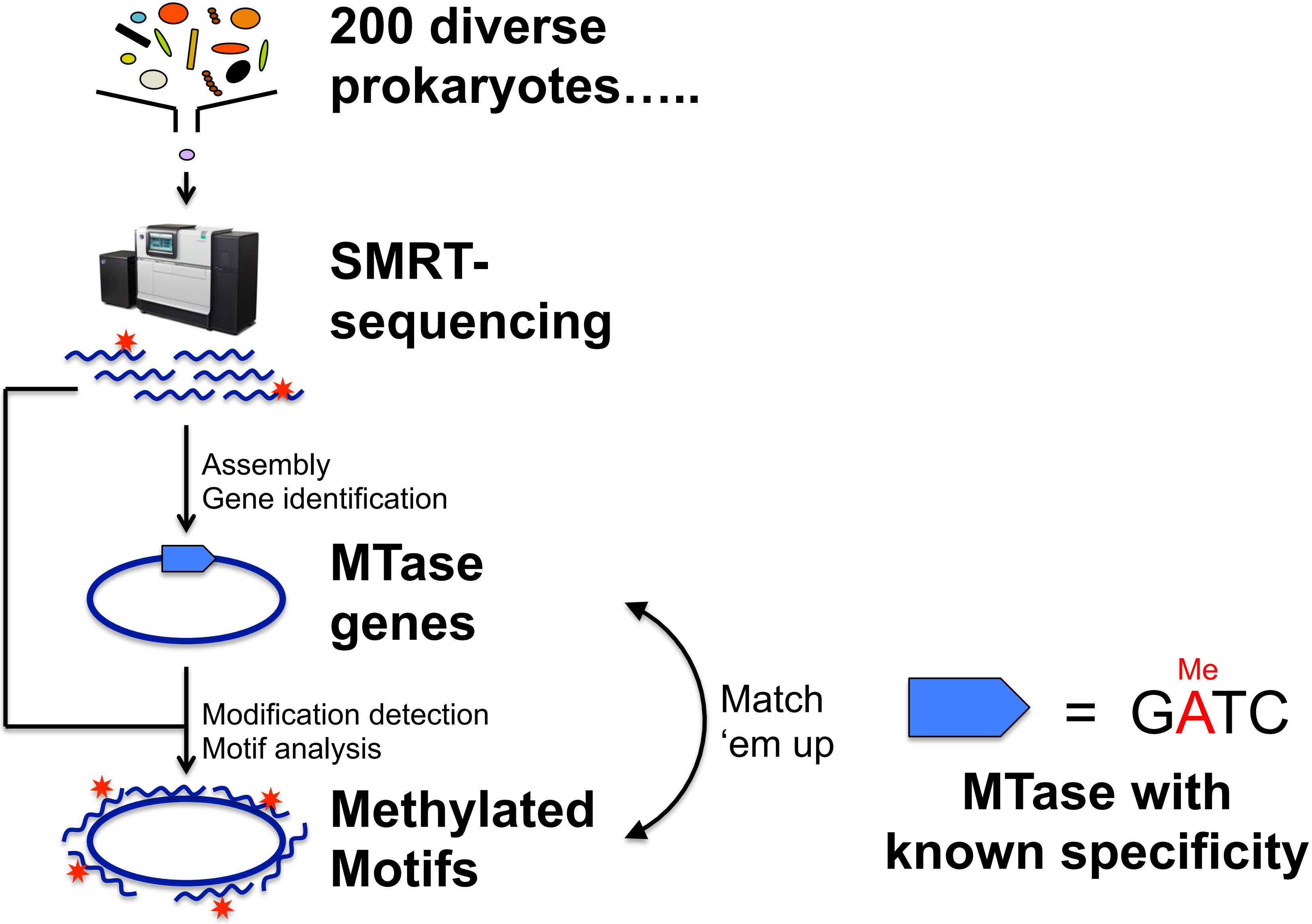


Delay in base incorporation opposite methyl adenine.

Modified DNA template



The Epigenomic Landscape of Bacteria



200 diverse prokaryotes…..

SMRT-sequencing

Assembly
Gene identification

MTase genes

Modification detection
Motif analysis

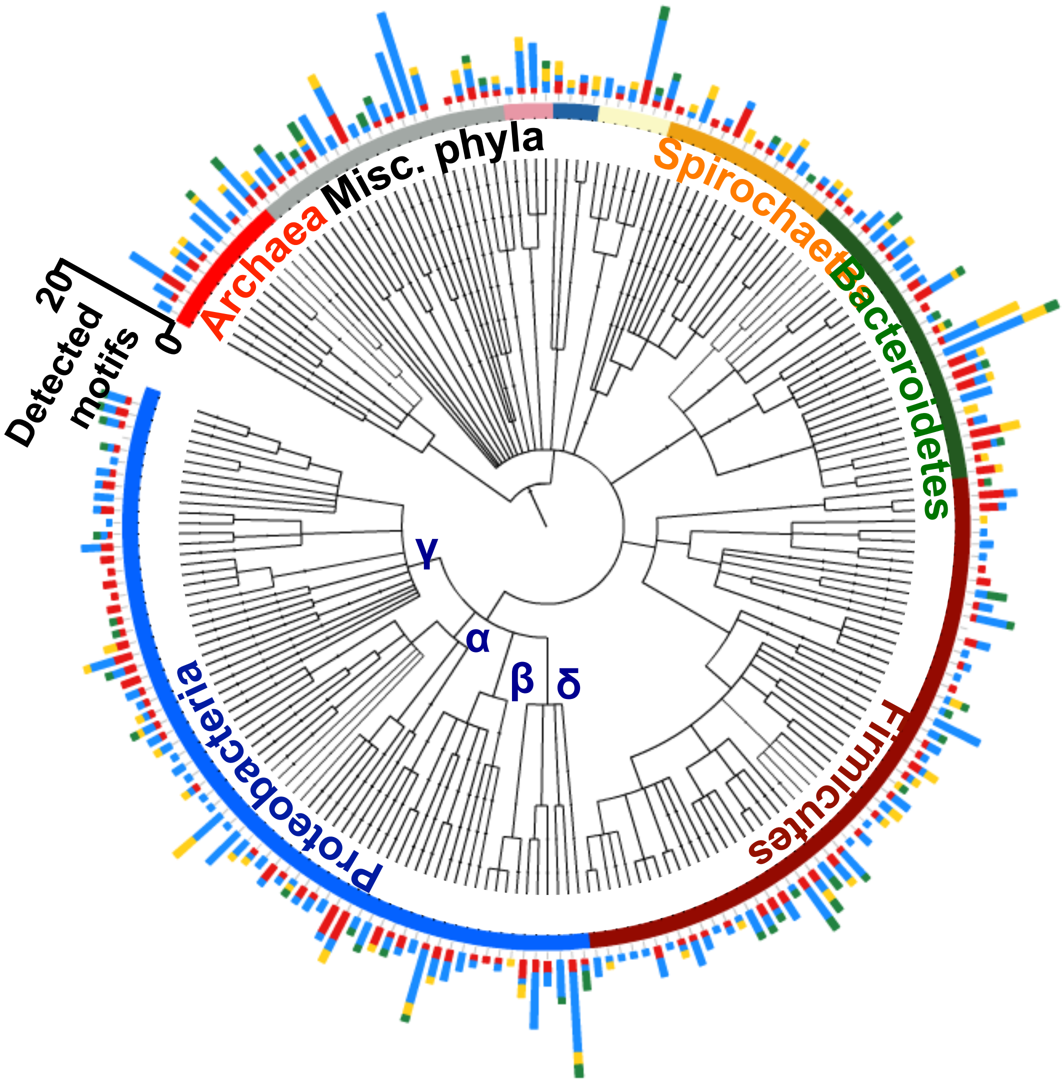
Methylated Motifs

Match 'em up

= G$\overset{\text{Me}}{\text{A}}$TC

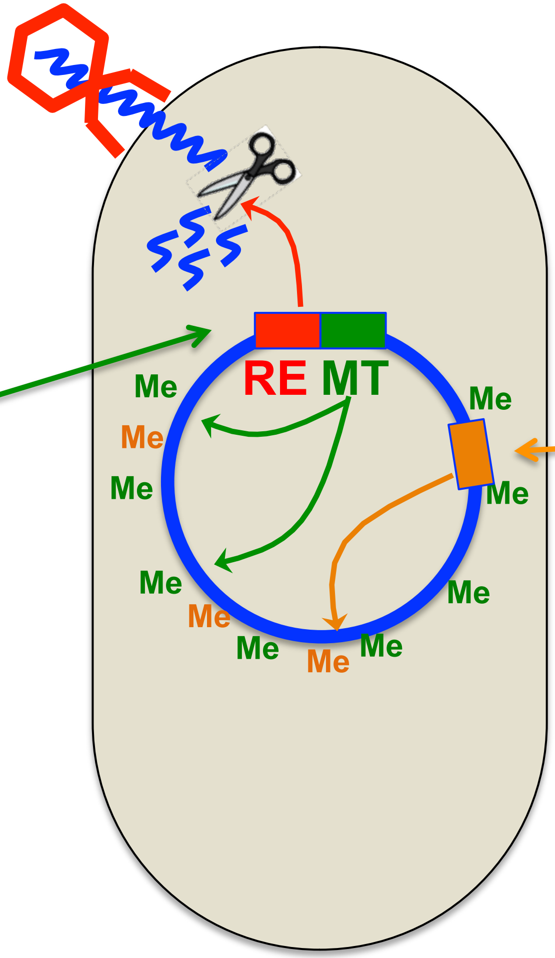
MTase with known specificity

Overview of 232 prokaryotic methylomes



415 MTase genes annotated

Many active MTases are ‘orphans’



276

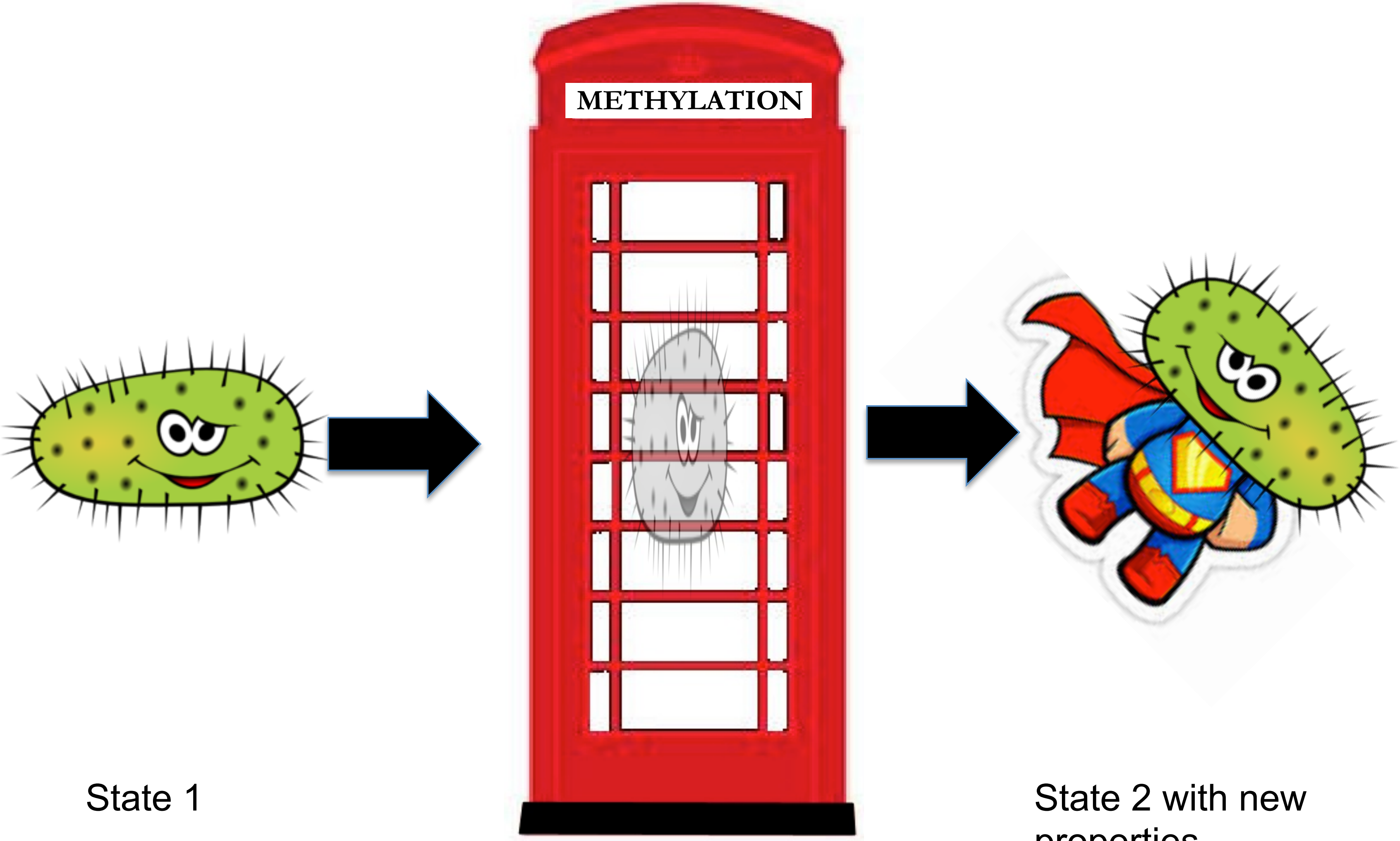
Restriction system MTases (67%)

139

‘Orphan’ MTases (33%)

Regulatory functions?

Methylation may controls gene regulation in some bacteria

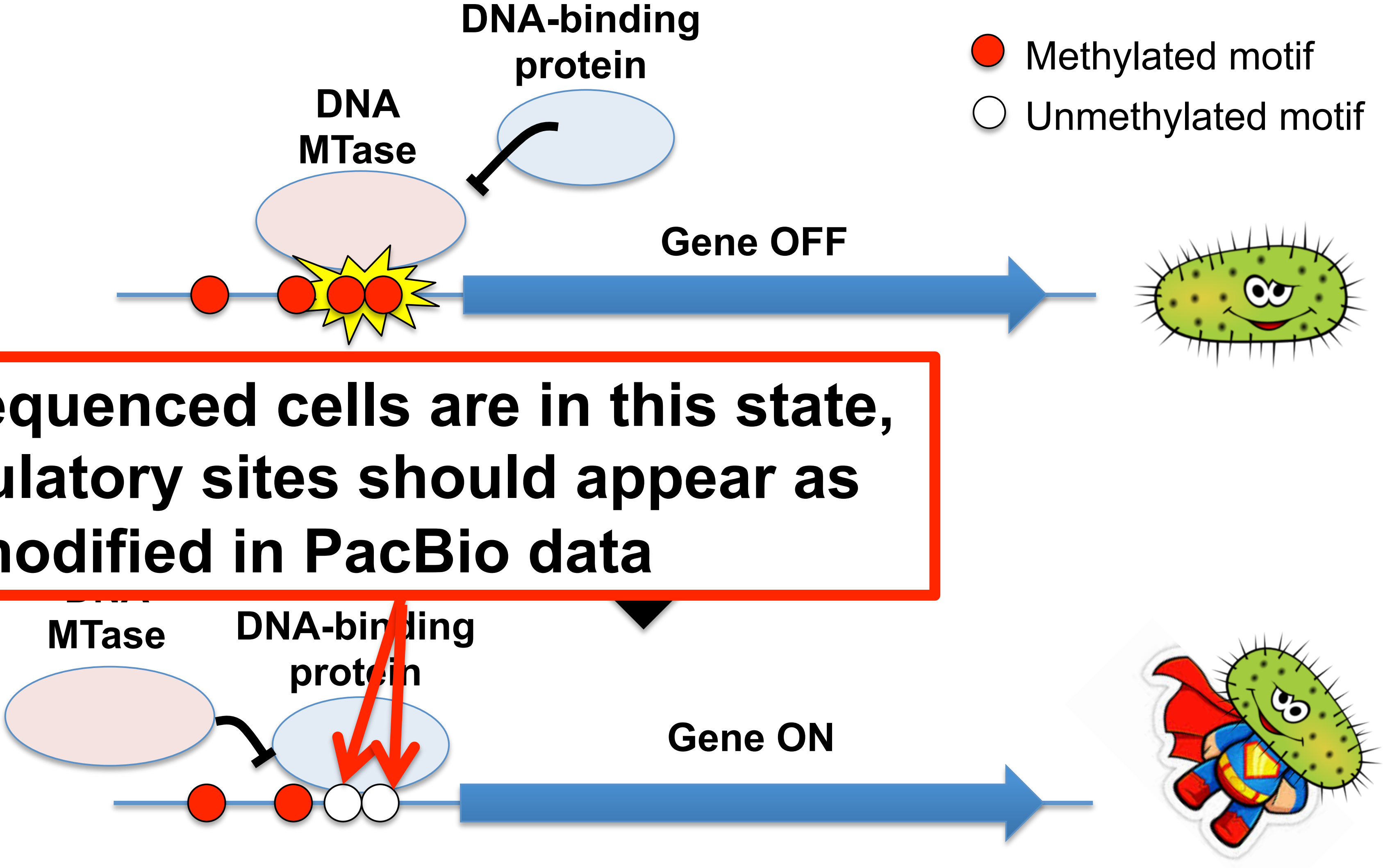


State 1

Change methylation state

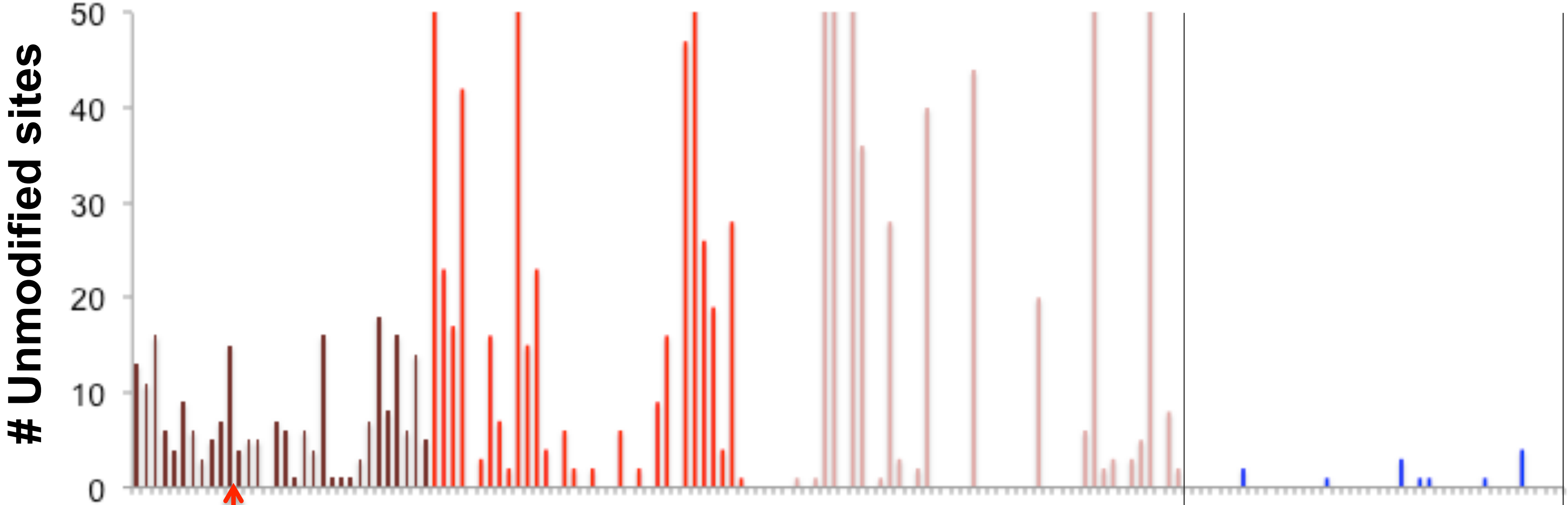
State 2 with new properties
(not necessarily good)

Model for gene regulation by DNA methylation



If sequenced cells are in this state, regulatory sites should appear as <u>un</u>modified in PacBio data

Orphan ‘Methyalses’ frequently associated with unmodified target sites in the genome



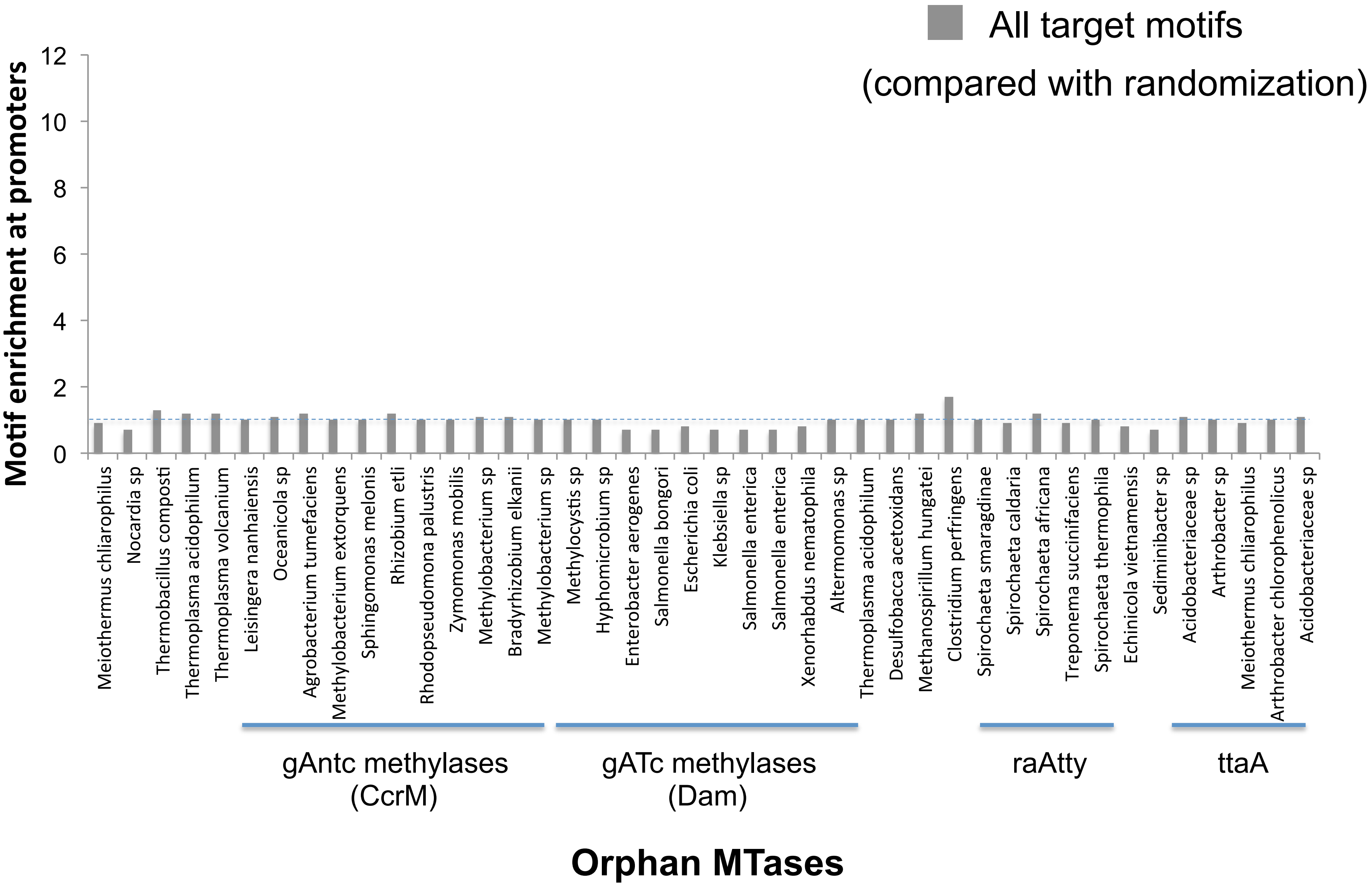
‘Orphan’ DNA MTases

RM system DNA MTases

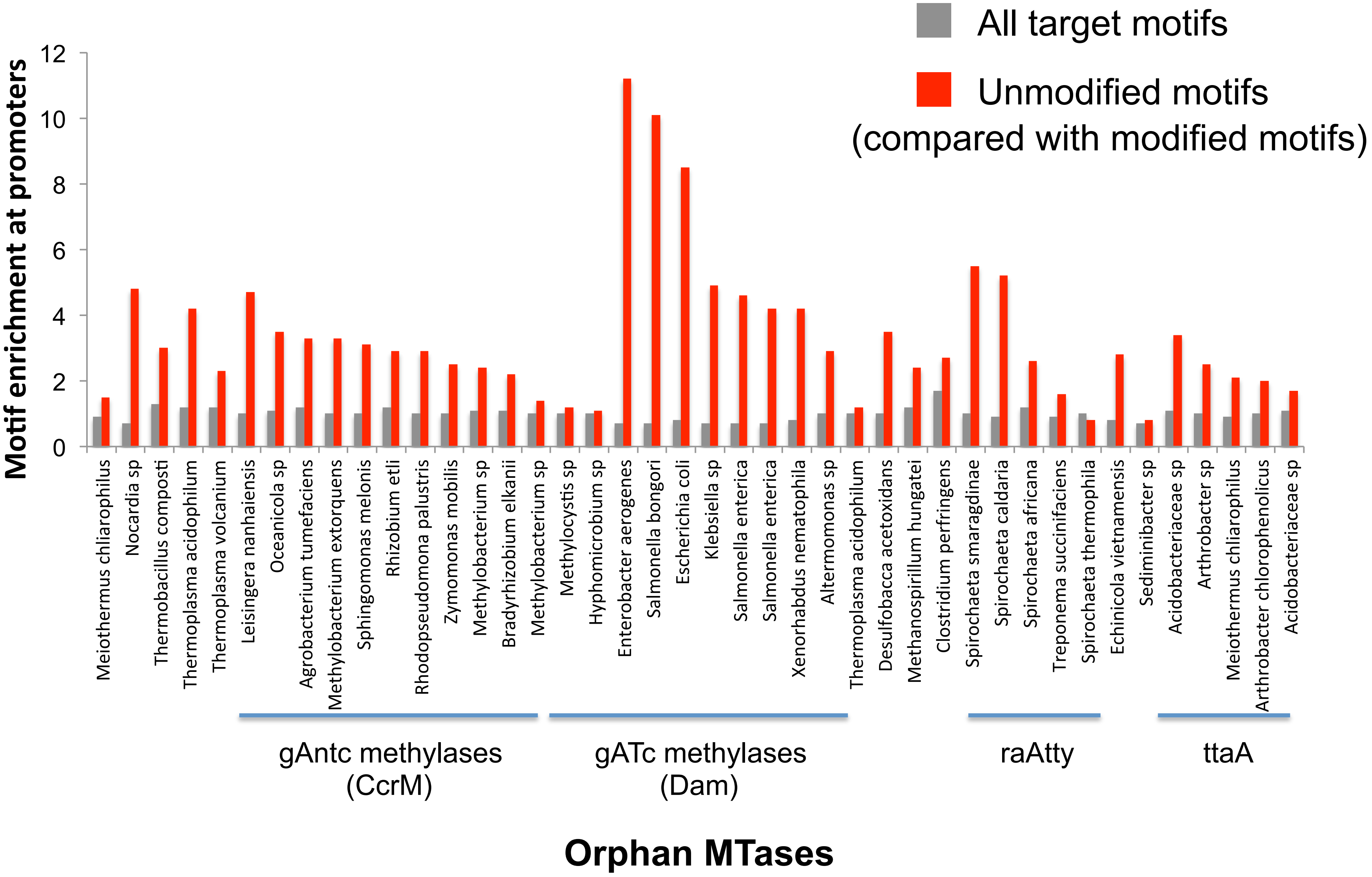
Includes 3 / 3 known regulatory sites in E.coli

Antigen43 (Waldron et al Mol microbiol 2002, Wallecha et al J. bacteriol 2002)

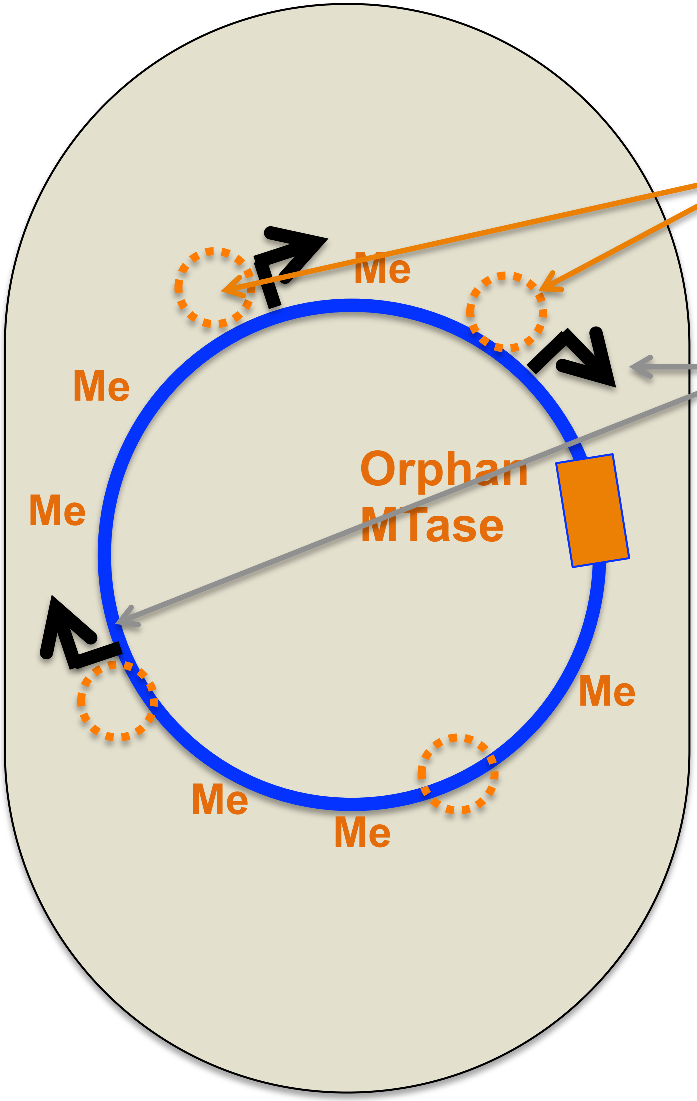
Unmethylated sites are enriched in gene regulatory regions



Unmethylated sites are enriched in gene regulatory regions



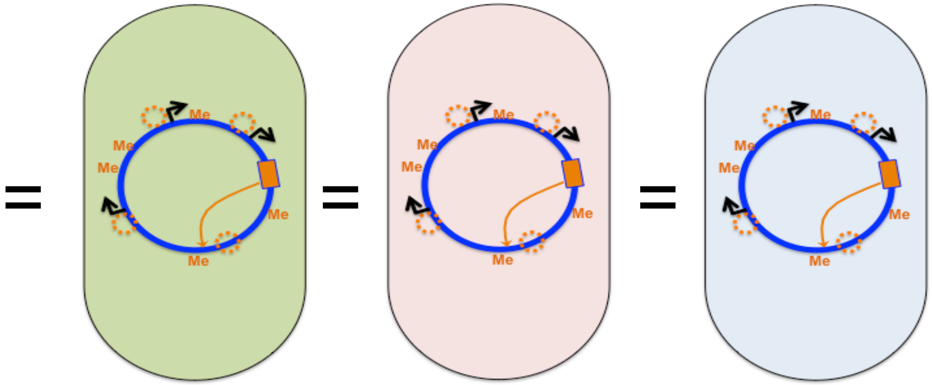
‘Orphan’ MTases have methylation patterns consistent with regulatory roles



Small number of target sites are UNmodified

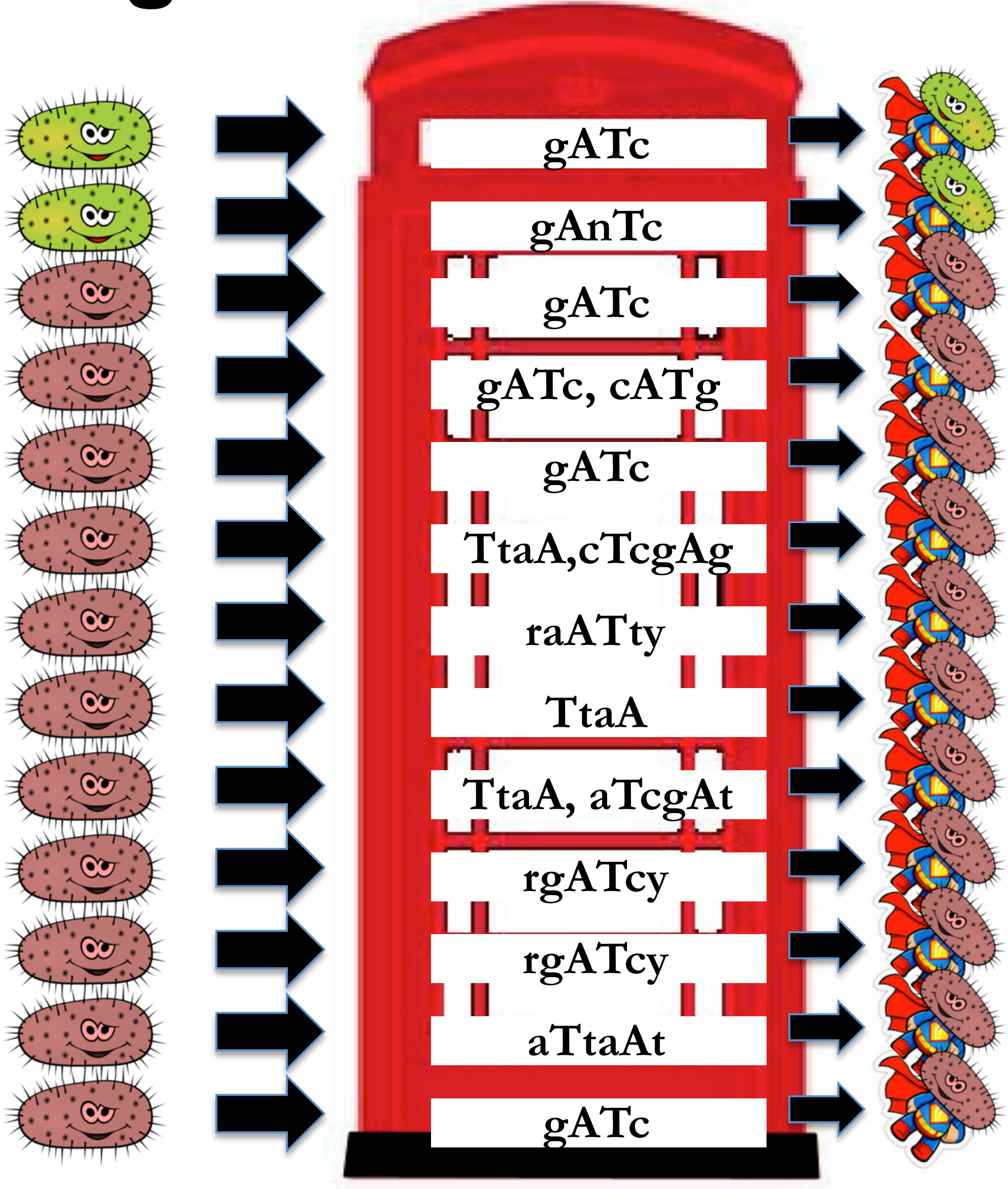
Unmodified sites are enriched near gene promoters

MTases and methylation patterns are conserved across related genomes



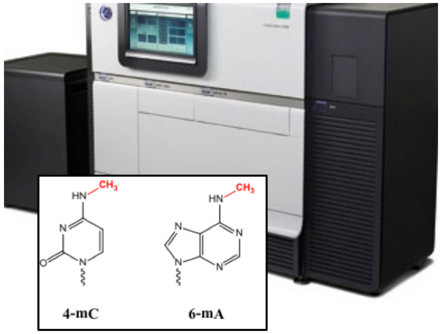
Validates regulatory modification at Antigen43 in E.coli (Waldron et al Mol microbiol 2002, Wallecha et al J. bacteriol 2002)

Methylation may play a widespread role in gene regulation in bacteria



Gammaproteobacteria	gATc
Alphaproteobacteria	gAnTc
Clostridia	gATc
Thermoplasmata	gATc, cATg
Chloroflexi	gATc
Deinococci	TtaA,cTcgAg
Spirochaetia	raATty
Acidobacteriia	TtaA
Actinobacteria	TtaA, aTcgAt
Cytophagia	rgATcy
Bacteroidetes	rgATcy
Bacilli	aTtaAt
Cyanobacteria	gATc

Bacterial Epigenomics Summary



We have generated 300 bacterial DNA base modification datasets on the PacBio platform

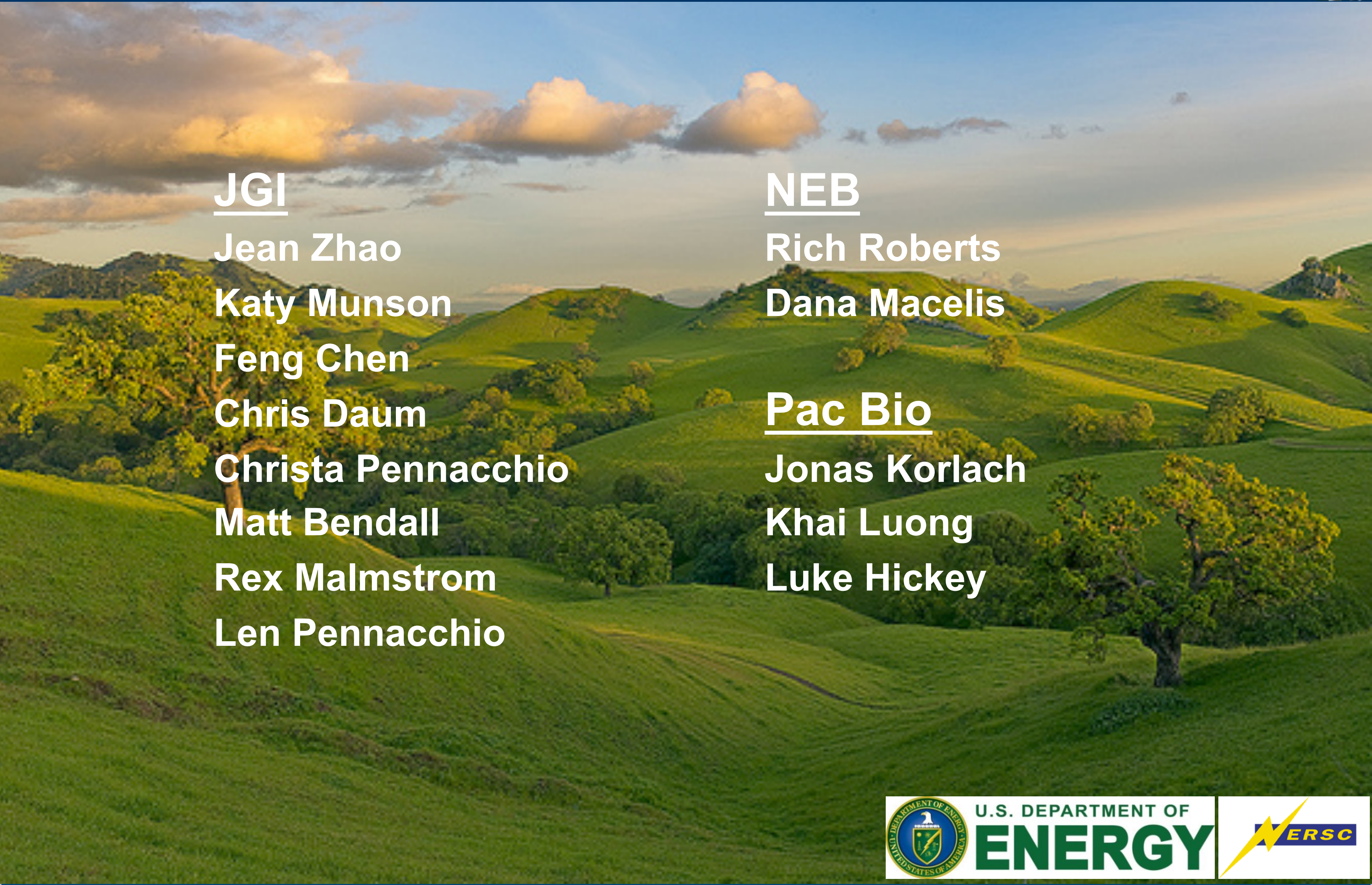
REBASE®

New insights into role of methylation in restriction systems and gene regulation

JGI
DOE JOINT GENOME INSTITUTE

Inviting user epigenome studies through the CSP program

Acknowledgements



JGI

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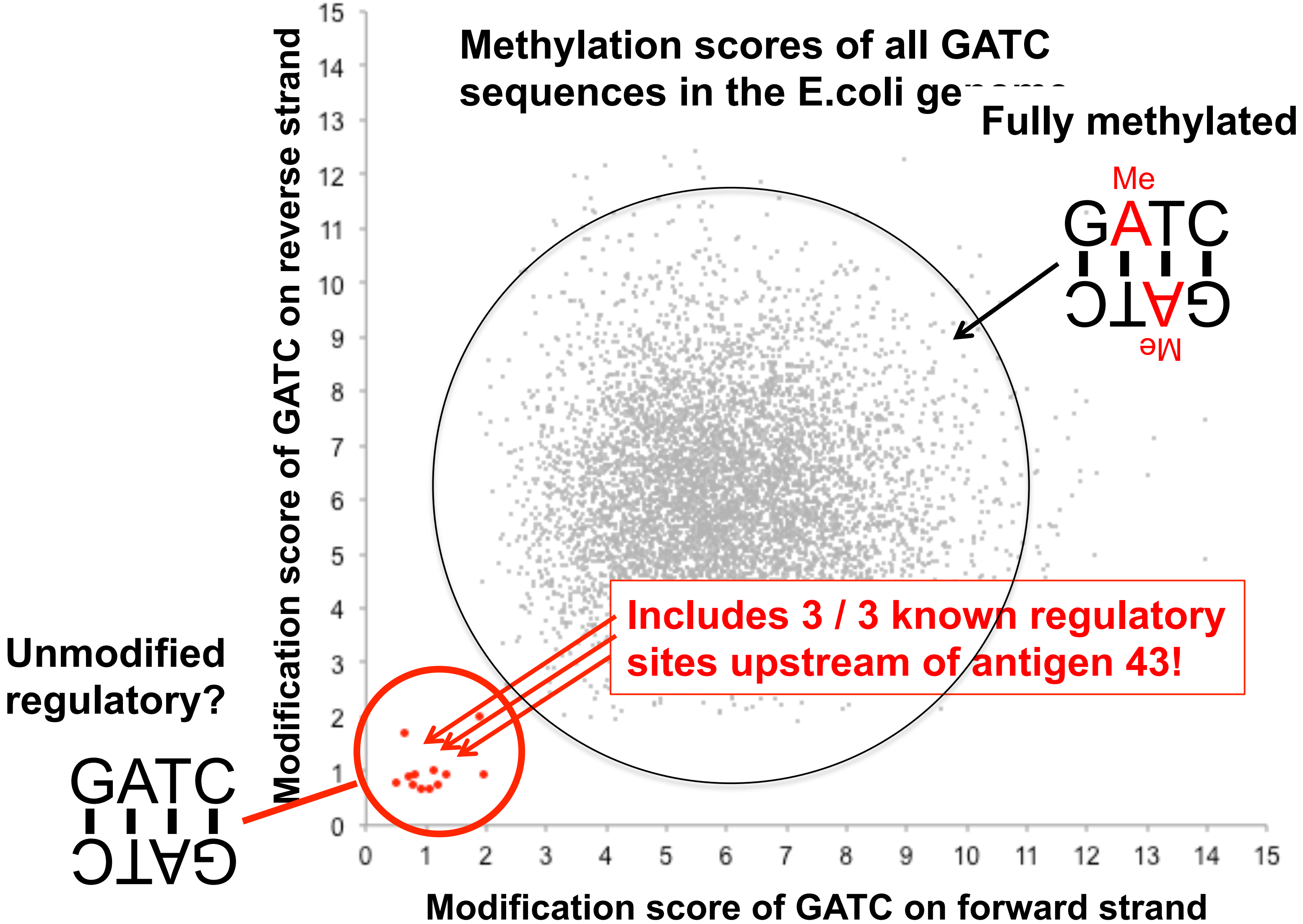
Luke Hickey

Known regulatory sites are detectable in PacBio data

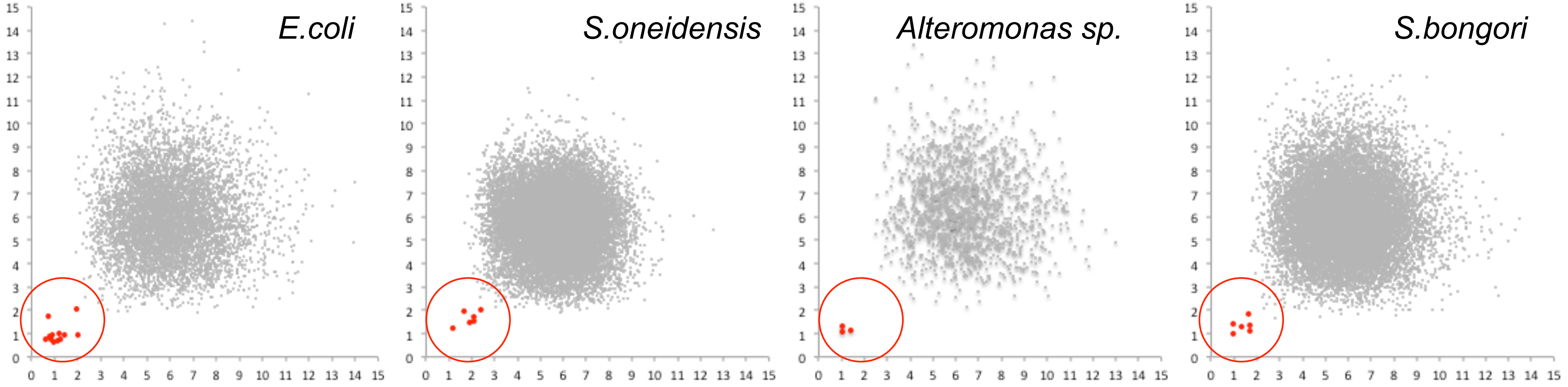
e.g. antigen 43 gene locus in *E. Coli*



Antigen43 (Waldron et al Mol microbiol 2002, Wallecha et al J. bacteriol 2002)

Unmodified GATC sites are detected in many sequenced gamma-proteobacteria ….

Four γ-proteobacteria with **regulatory** GATC modification



… but not when GATC is associated with a restriction system