RNA modifications and decoding

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The genetic code is
- **redundant**
- **quasi-universal**

The genetic code is

- **it is the result of molecular recognition during biological evolution**

- **its representation is arbitrary**

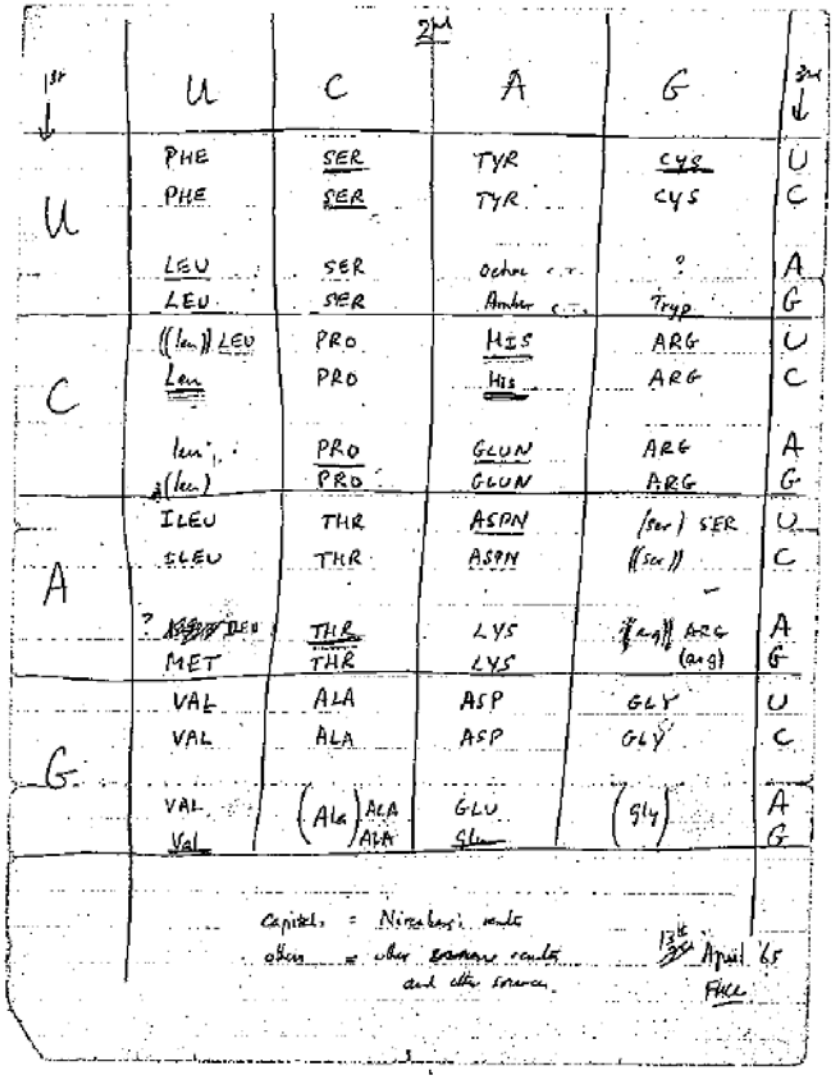
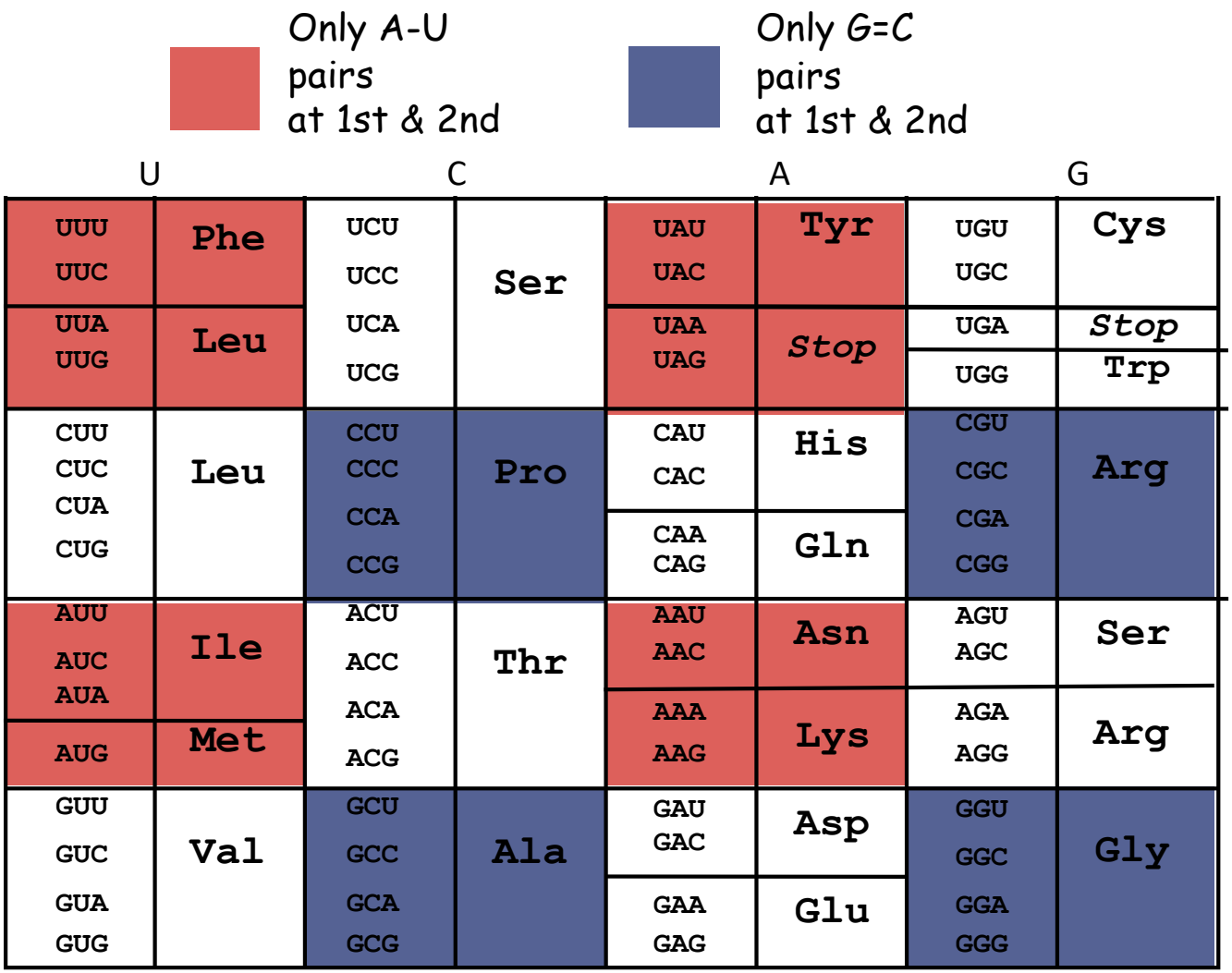


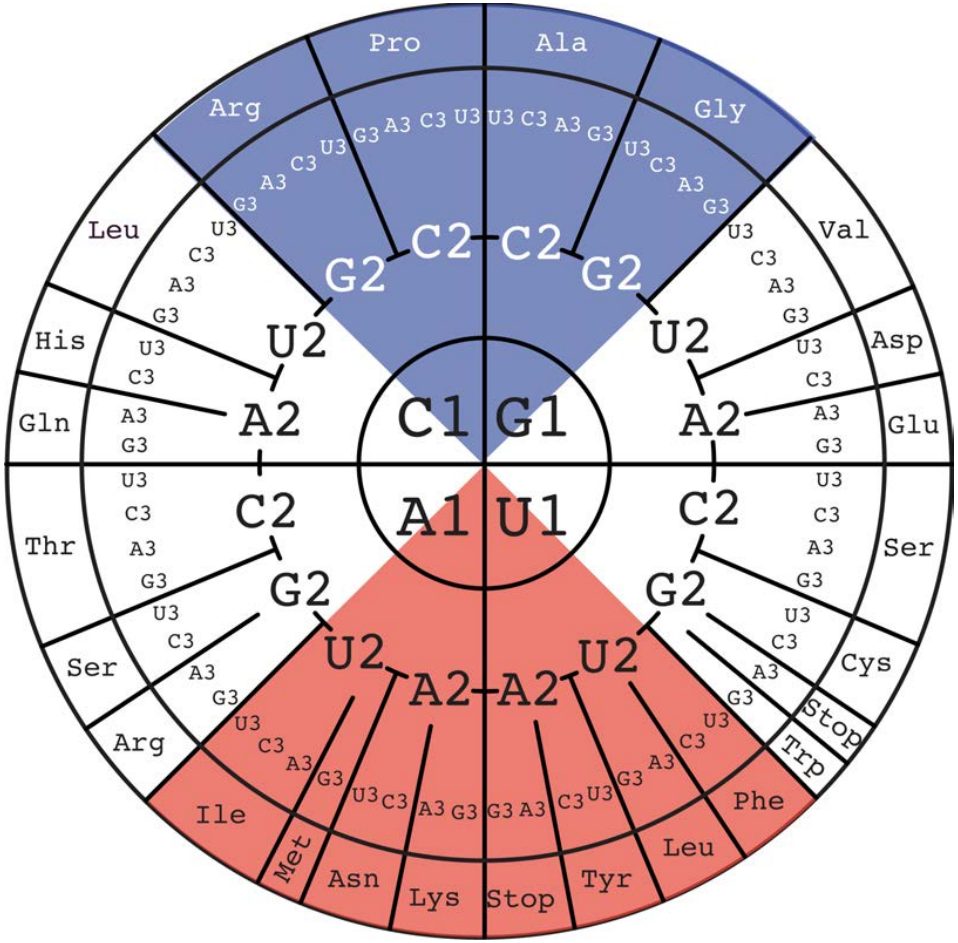
Figure 15.2 Crick's rough sketch of his checkerboard showing the stage reached in solving the genetic code in April 1965.

From
« FRANCIS CRICK, Hunter of Life's Secrets »
Robert Olby CSHLP, 2009.


Only A-U pairs at 1st & 2nd
Only G=C pairs at 1st & 2nd
U
C
A
G
UUU Phe
UUC
UCU Ser
UCC
UCA
UCG
UAU Tyr
UAC
UGU Cys
UGC
UUA Leu
UUG
UAA Stop
UAG
UGA Stop
UGG Trp
CUU Leu
CUC
CUA
CUG
CCU Pro
CCC
CCA
CCG
CAU His
CAC
CAA Gln
CAG
CGU Arg
CGC
CGA
CGG
AUU Ile
AUC
AUA
AUG Met
ACU Thr
ACC
ACA
ACG
AAU Asn
AAC
AAA Lys
AAG
AGU Ser
AGC
AGA Arg
AGG
GUU Val
GUC
GUA
GUG
GCU Ala
GCC
GCA
GCG
GAU Asp
GAC
GAA Glu
GAG
GGU Gly
GGC
GGA
GGG

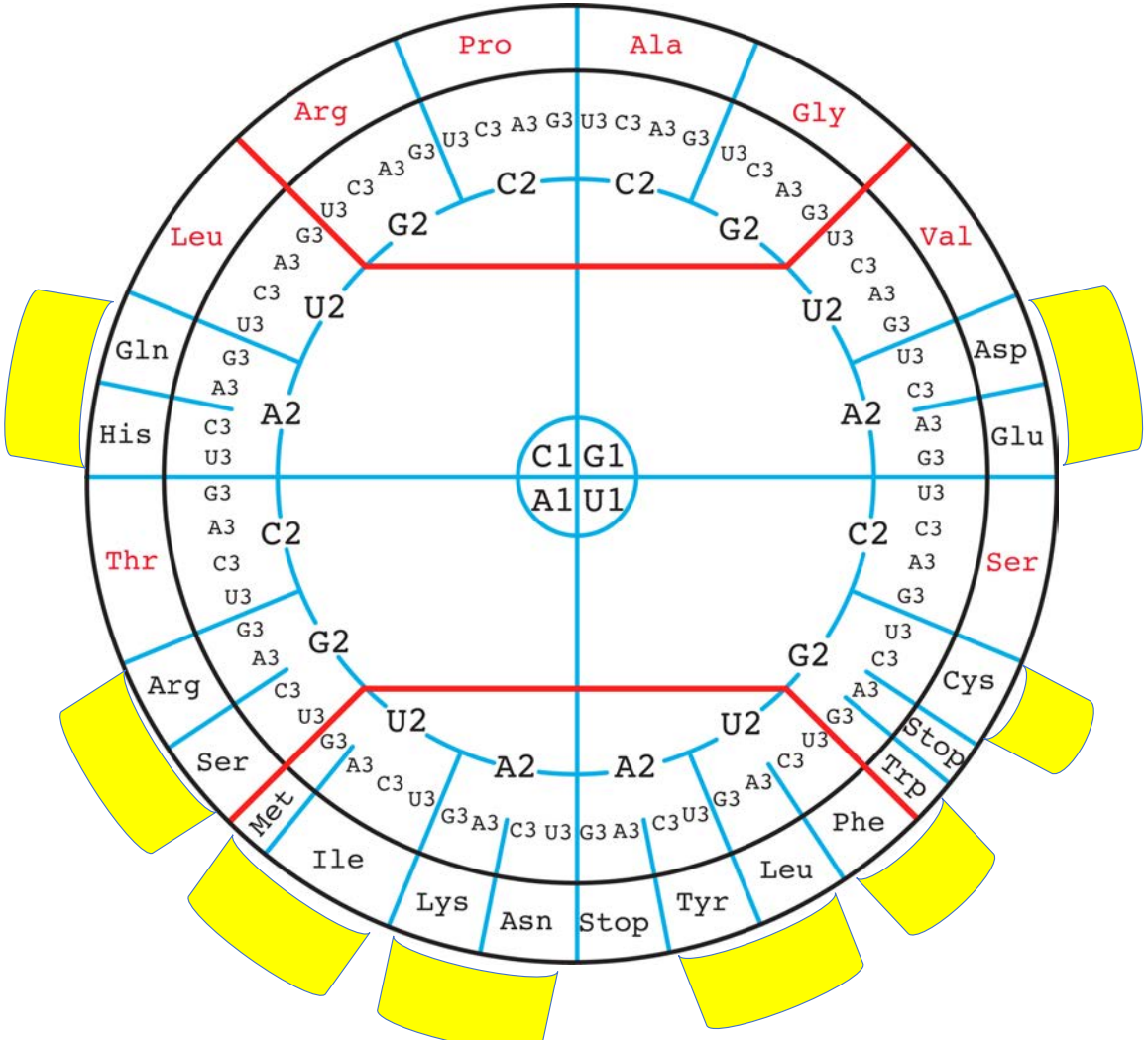
How to optimize the ribosome « rhythm »?
How to optimize protein synthesis and folding?

Increasing stability of network interactions

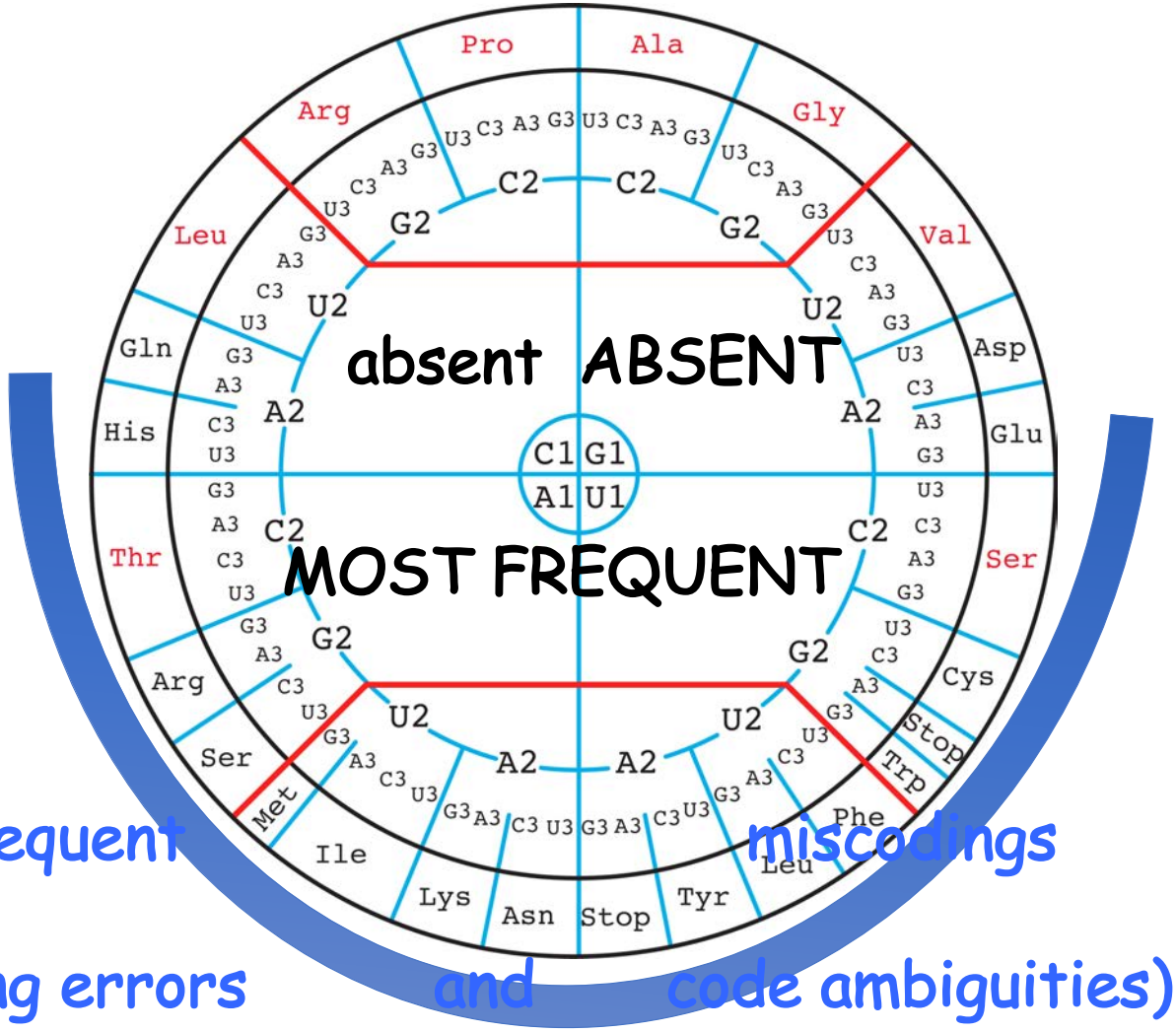


Grosjean, H. and E. Westhof (2016). "An integrated, structure- and energy-based view of the genetic code." Nucleic Acids Res **44**: 8020-8040.

STOP and 2-codons boxes mainly in the south



Code deviations, recoding, codon reassignments

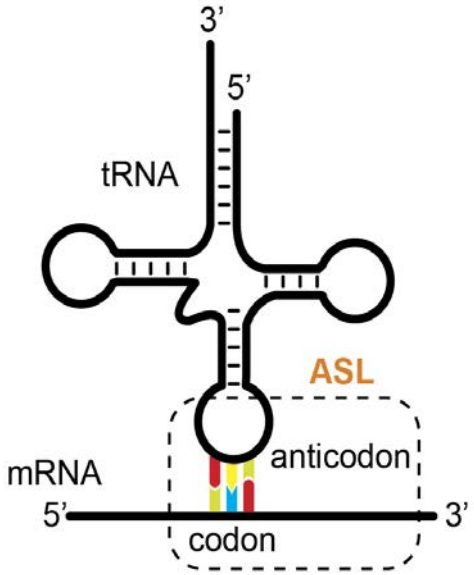


Most frequent miscodings

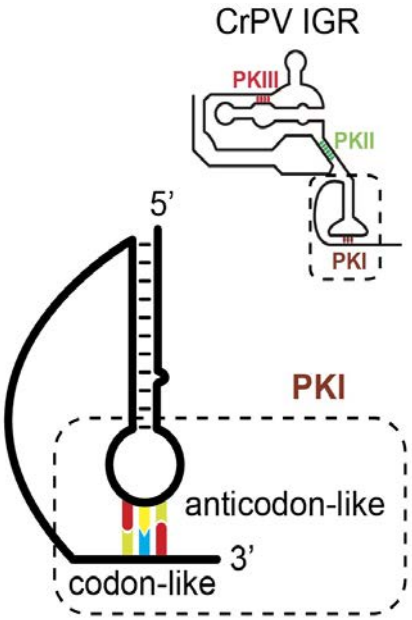
(decoding errors and code ambiguities)

A microfluidic-based assay recapitulates eukaryotic ribosomal translation

Model system uses the intergenic IRES of Cricket Paralysis Virus coupled with the GFP as reporter

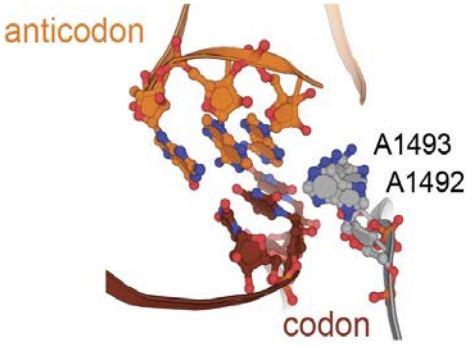


INTERmolecular
(2 molecules)

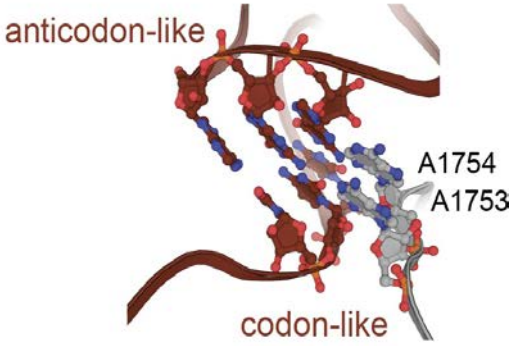


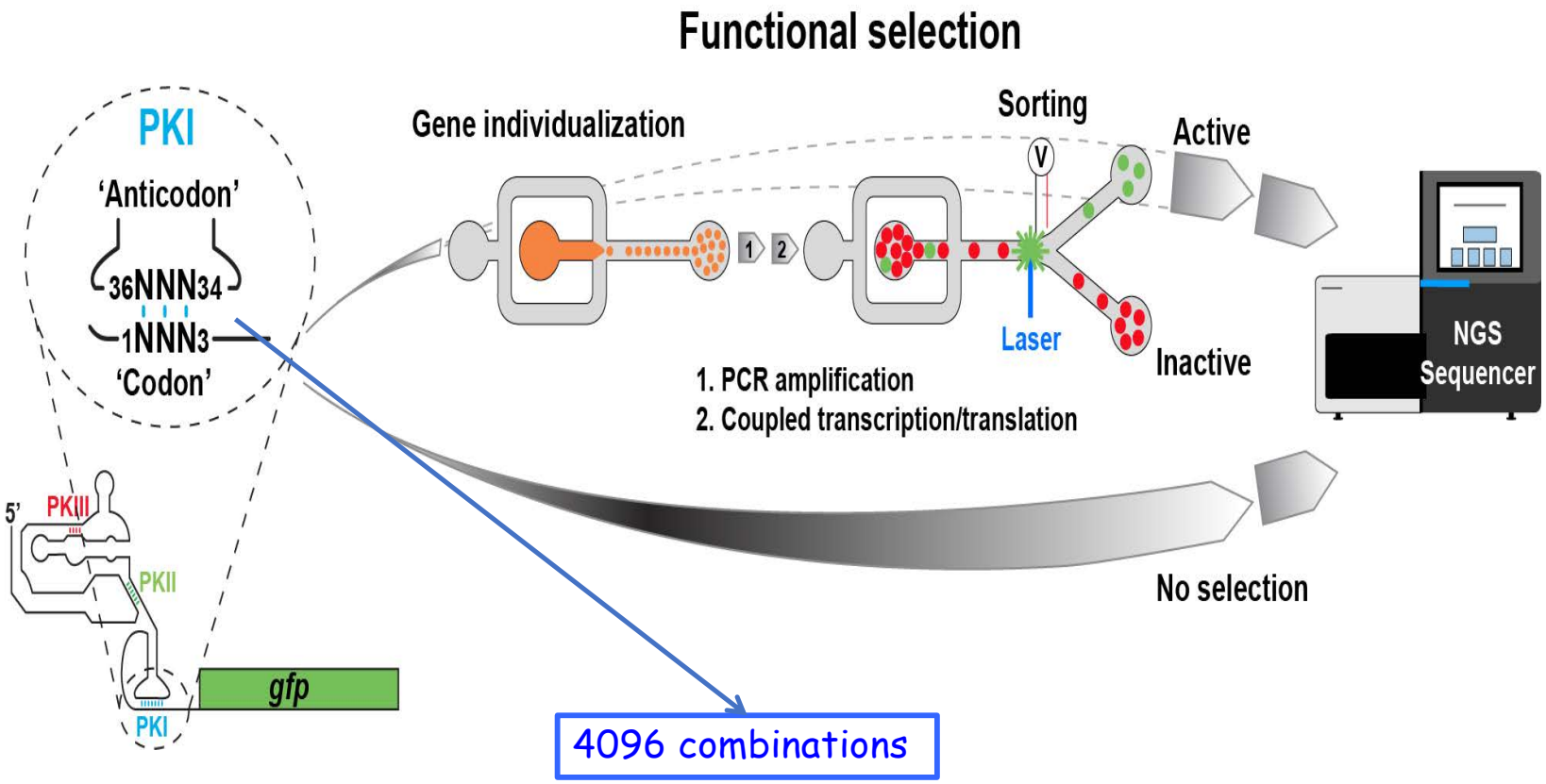
INTRAmolecular
(1 molecule pseudoknot)

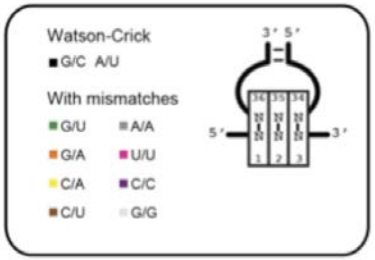
ASL



PKI




Functional selection
PKI
'Anticodon'
36NNN34
1NNN3
'Codon'
5'
PKIII
PKII
PKI
gfp
Gene individualization
1
2
Sorting
V
Laser
Active
Inactive
1. PCR amplification
2. Coupled transcription/translation
NGS
Sequencer
No selection
4096 combinations



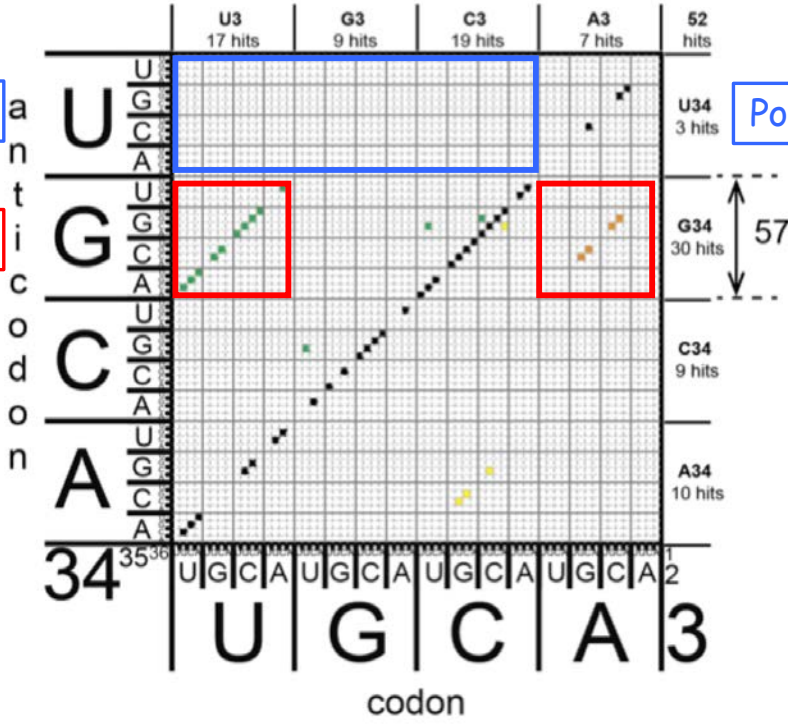
‘Stringent’ selection

U34oG3 NOT present

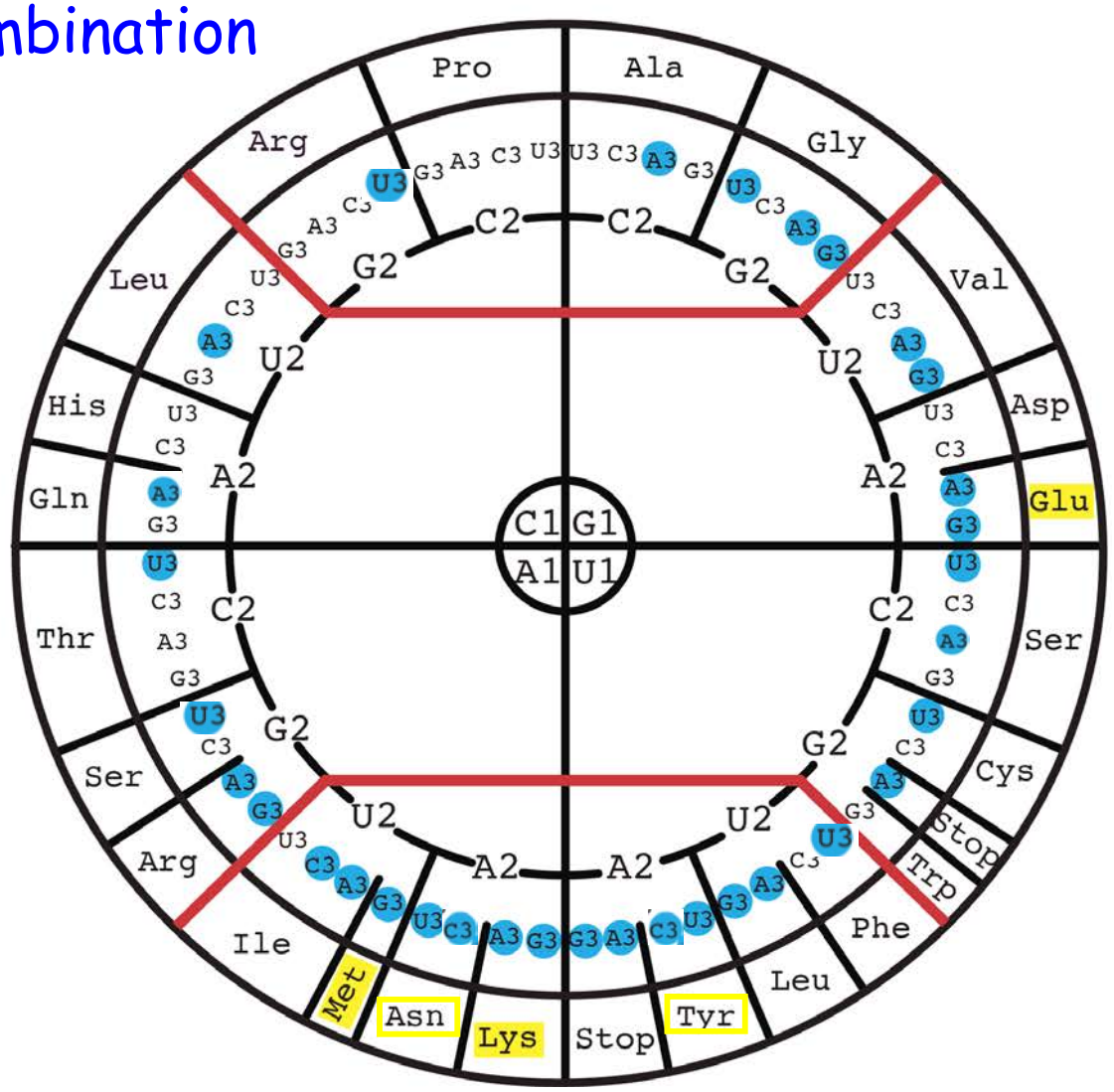
G34oU3 present

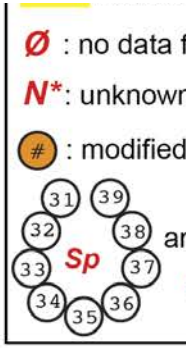
Poor decoding with U34

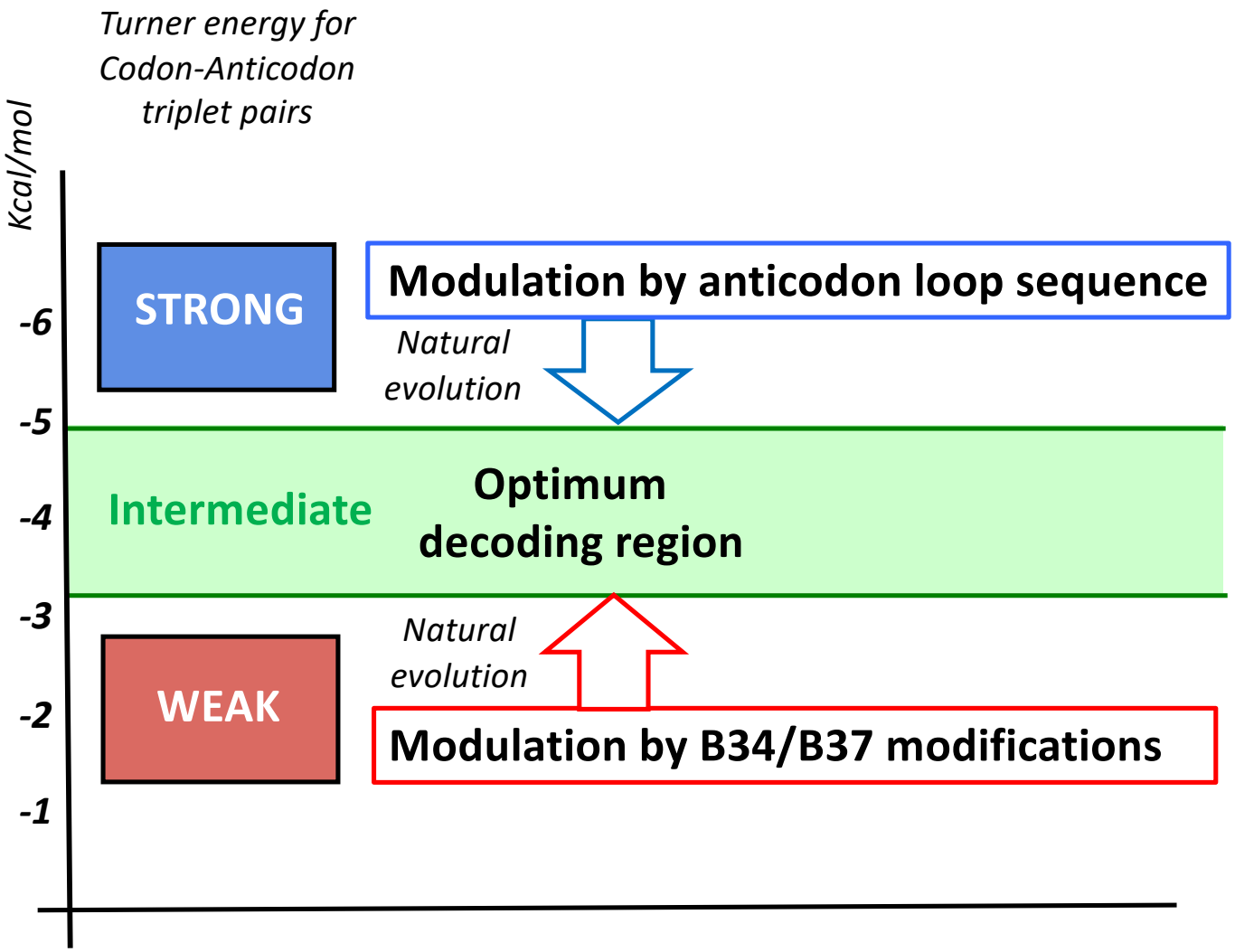
G34oA3 present

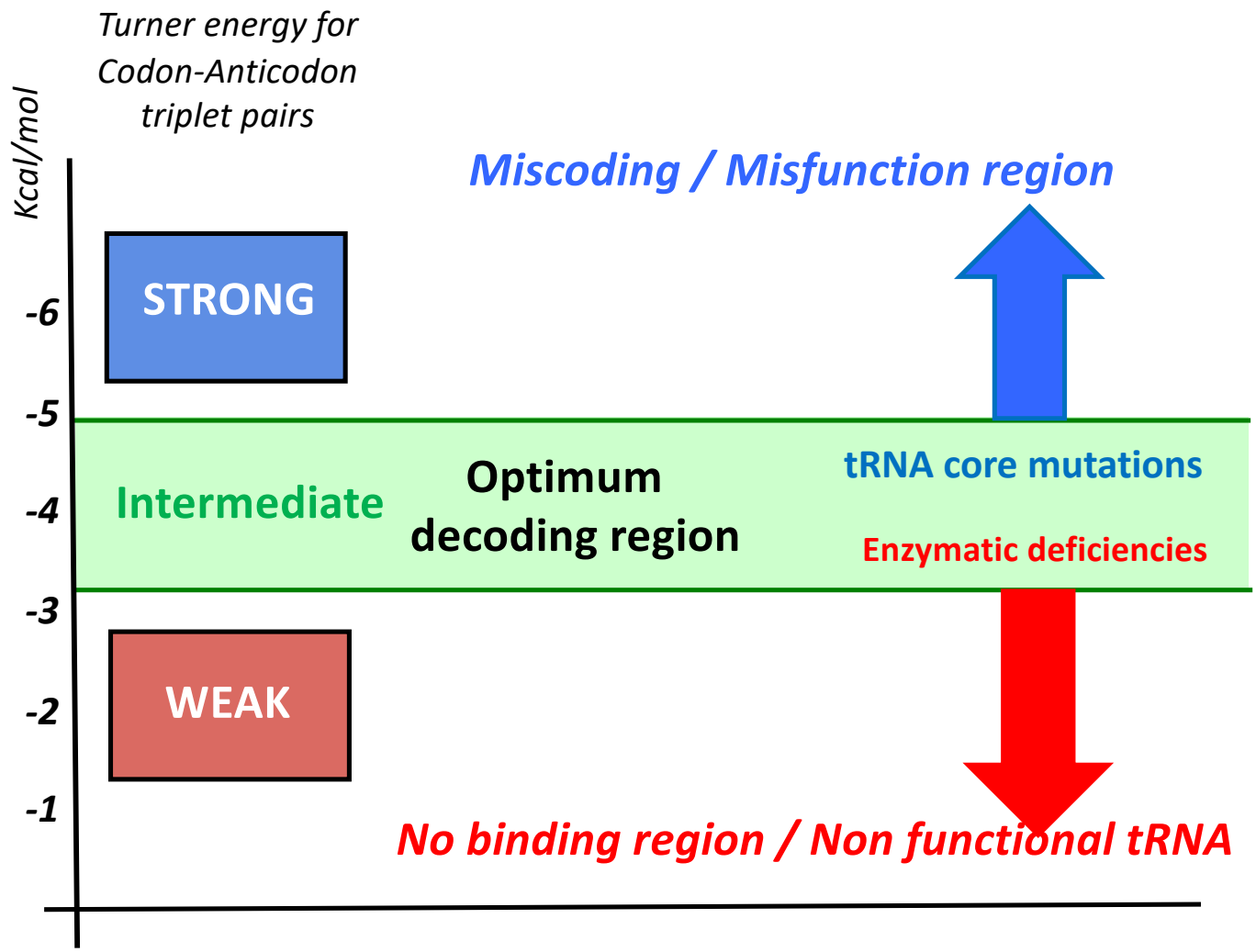


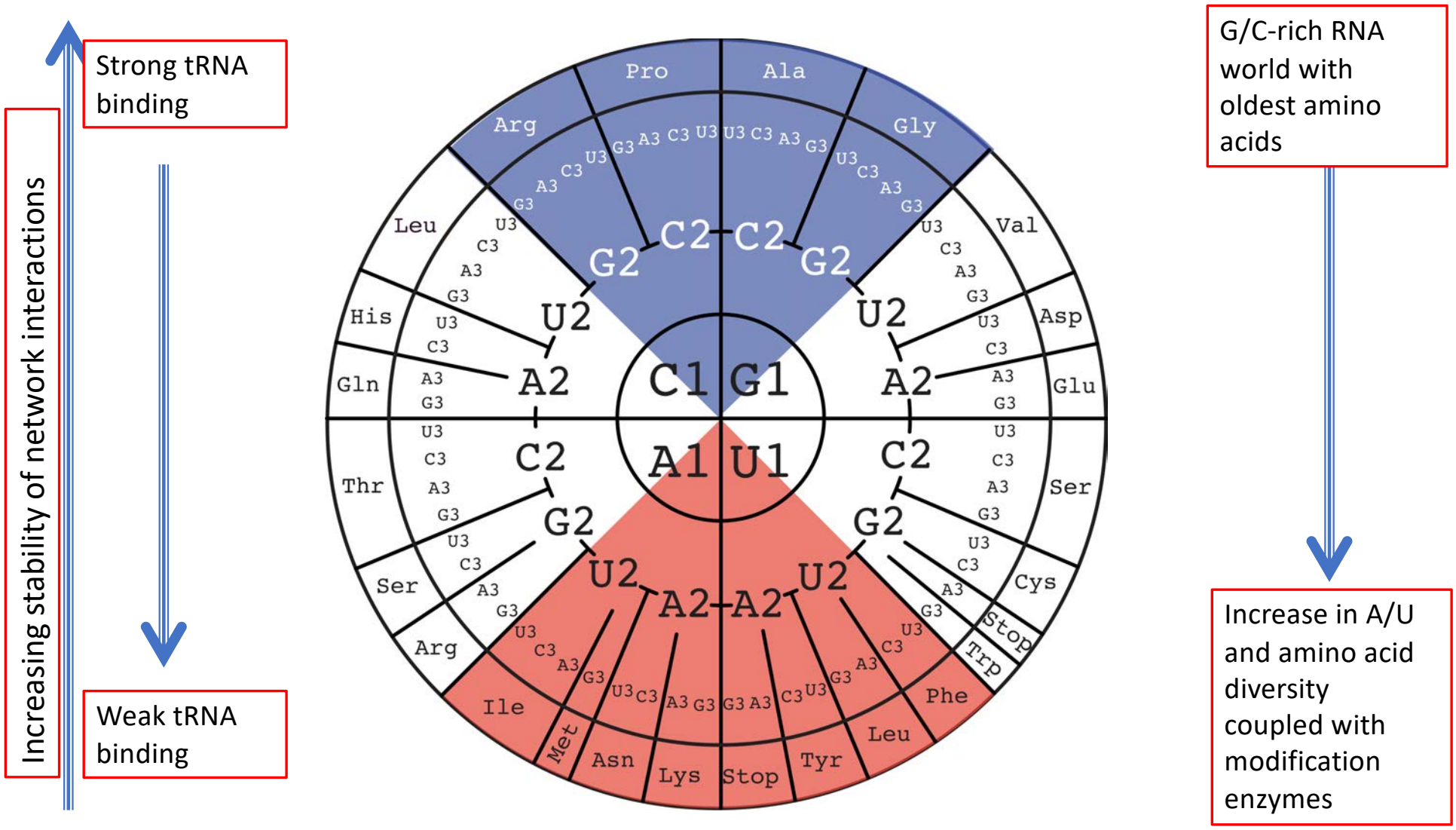
BLUE = Absent codon/anticodon combination






Turner energy for
Codon-Anticodon
triplet pairs
Kcal/mol
-6
-5
-4
-3
-2
-1
STRONG
Modulation by anticodon loop sequence
Natural
evolution
Intermediate
Optimum
decoding region
Natural
evolution
WEAK
Modulation by B34/B37 modifications


Turner energy for
Codon-Anticodon
triplet pairs
Kcal/mol
-6
-5
-4
-3
-2
-1
STRONG
Miscoding / Misfunction region
Intermediate
Optimum
decoding region
tRNA core mutations
Enzymatic deficiencies
WEAK
No binding region / Non functional tRNA



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