Appendix A : Media and some general solutions

A1 Media

All final volumes were made up to one litre with deionised sterile water. All media was sterilised by autoclaving for 10 minutes at 121^{o}C.

A1.1 Luria Bertani broth (LB)
10 g tryptone powder, 5 g yeast extract, 10 g sodium chloride

A1.2 Luria Bertani agar (LA)
10 g tryptone powder, 5 g yeast extract, 10 g sodium chloride, 15 g agar powder

A1.3 Middlebrook 7H9 broth (MADC-Tw)
4.7 g Middlebrook 7H9 media and 2 mL glycerol. To this, ADC (50 g/L albumin, 20 g/L dextrose and 0.04 g/L catalase as supplied by the manufacturer) and 5.0 mL of filter sterilised 20% Tween 80 were added aseptically after autoclaving

A1.4 Middlebrook 7H10 agar plates
19 g Middlebrook 7H10 media and 5 mL glycerol. To this, OADC (0.5 g/L oleic acid, 50 g/L albumin, 20 g/L dextrose and 0.04 g/L catalase as supplied by the manufacturer) was added aseptically after autoclaving

A1.5 2TY broth
16 g tryptone powder, 10 g yeast extract, 5 g sodium chloride

A2 General Solutions

All final volumes were one litre unless otherwise specified. All solutions were filter sterilised using a 0.22 µM filter

A2.1 Antibiotic stocks

A2.1.1 Ampicillin: 100 mg/mL made up in 50% ethanol and stored at -20^{o}C
A2.1.2 Gentamicin: 10 mg/mL made up in 50% ethanol and stored at -20^{o}C
A2.1.3 Hygromycin B: 50 mg/mL supplied in phosphate buffered saline and stored at 4^{o}C
A2.1.4 Kanamycin: 50 mg/mL made up in sterile water and stored at 4^{o}C
A2.1.5 Rifampicin: 200 mg/mL made up in DMF and stored in dark glass at 4^{o}C

A2.2 L-Histidine

100 mg/mL made up in sterile water and stored at 4^{o}C

A2.3 Solution I (plasmid isolation)

0.5 M glucose, 50 mM Tris-HCl pH 8.0, 10mM EDTA

A2.4 Solution II (plasmid isolation)

0.2 M NaOH, 1% SDS

A2.5 Solution III (plasmid isolation)

3 M potassium acetate, pH 5.5

A2.6 Cetyltrimethylammoniumbromide (CTAB) solution

10% cetyltrimethylammoniumbromide prepared in 0.7 M NaCl

A2.7 TE buffer

10 mM Tris-HCl pH 8.0, 1 mM EDTA pH 7.6

A2.8 Loading dye

Recipe for 15 mL stock solution: 4.5mL glycerol, 10.5mL deionised sterile distilled water, 0.04g bromophenol blue

Appendix B : Plasmid maps

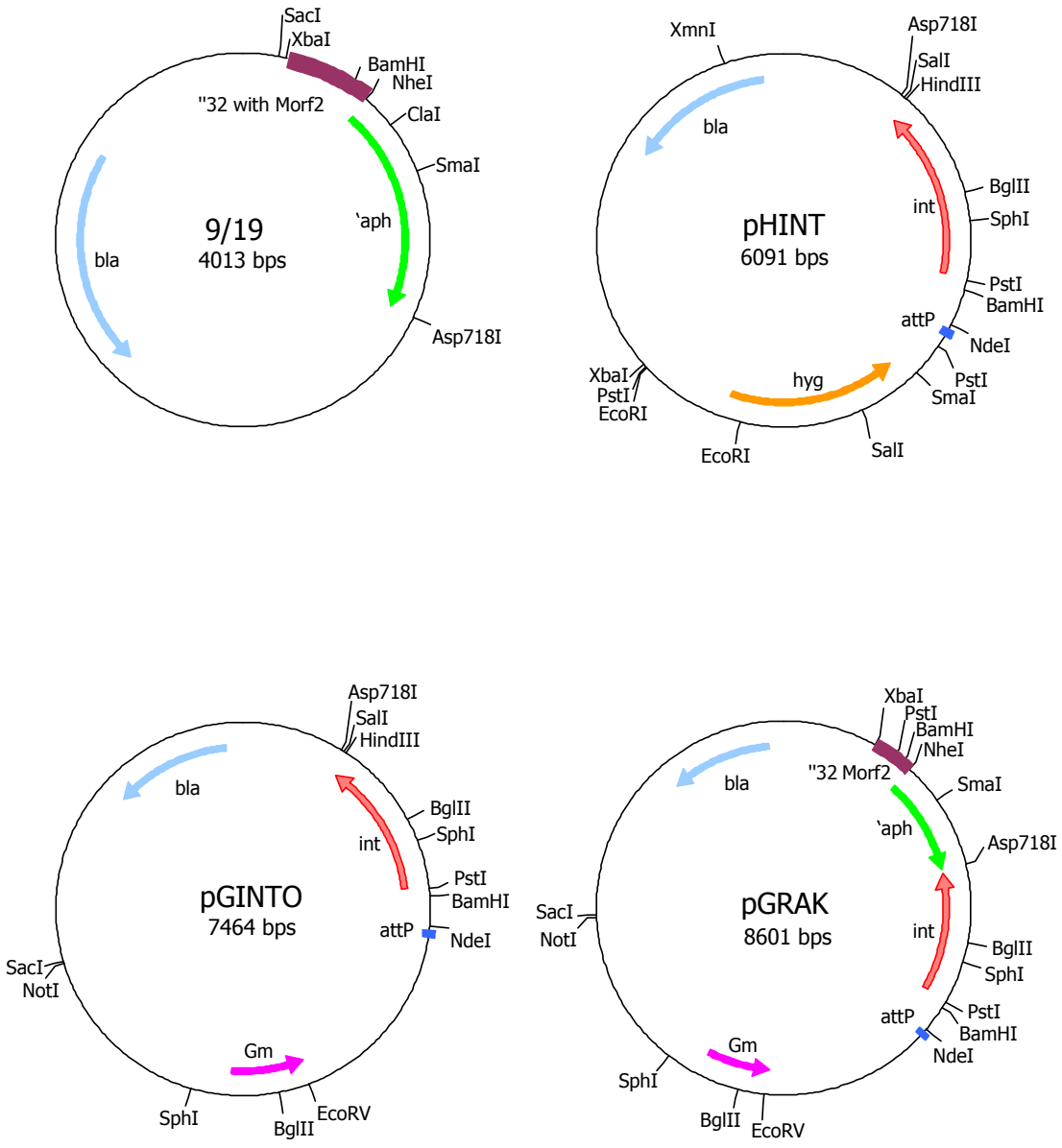


Figure B1: Plasmids p9/19, pHINT, pGINTO and pGRAK.

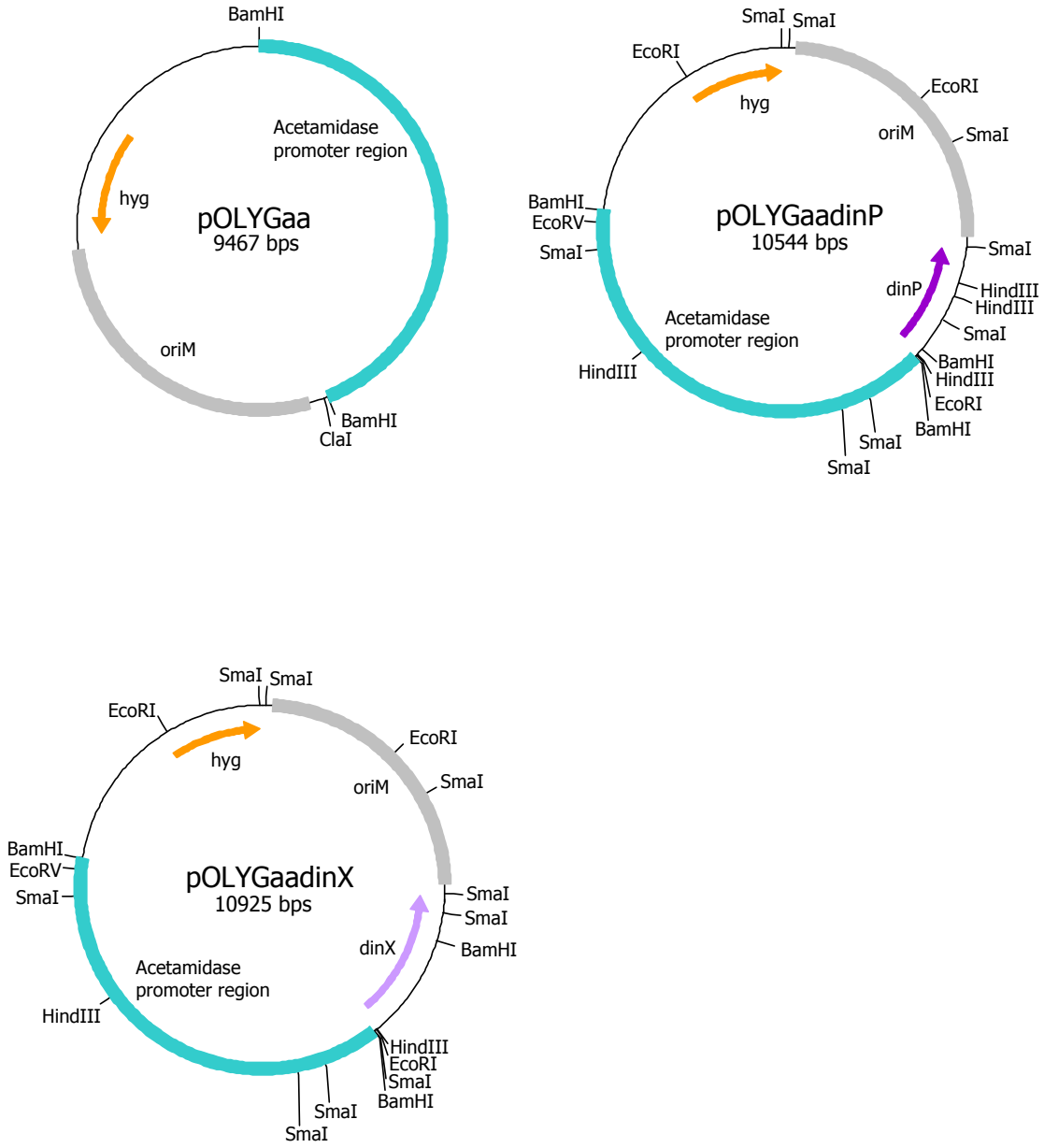
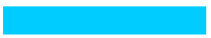
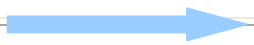
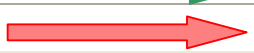
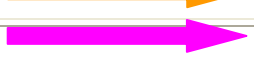


Figure B2: Plasmids pOLYGaa, pOLYGaadinP and pOLYGaadinX.

Table B1: Symbol definitions of the plasmid maps in Appendix B

Symbol	Definition
	*attP* site on plasmid that integrates with *attB* site on bacterial chromosome
	"32 region flanked by *Xba*I and *Nhe*I containing Morf2 construct
	*Bam*HI cassette containing acetamidase promoter
	Origin of replication (OriM) of plasmid
	Repeat 1 (R1) of Morf2 construct
	Distal repeat 3 (dR3) of Morf2 construct
	Proximal repeat 2 (pR2) of Morf2 construct
	3' PCR region used to generate ΔrecA and ΔL knockout (KO) plasmids
	5' PCR region used to generate ΔrecA and ΔL KO plasmids
	*bla* gene encoding β-lactamase for Ampicillin resistance
	'aph cassette containing Km resistance gene without its own ATG codon
	complete aph cassette containing Km resistance gene
	*int* gene encoding factors used to integrate with bacterial chromosome
	*hyg* cassette encoding Hygromycin resistance factors
	*Gm* cassette encoding Gentamicin resistance factors
	dinP gene under control of the acetamidase promoter
	dinX gene under control of the acetamidase promoter

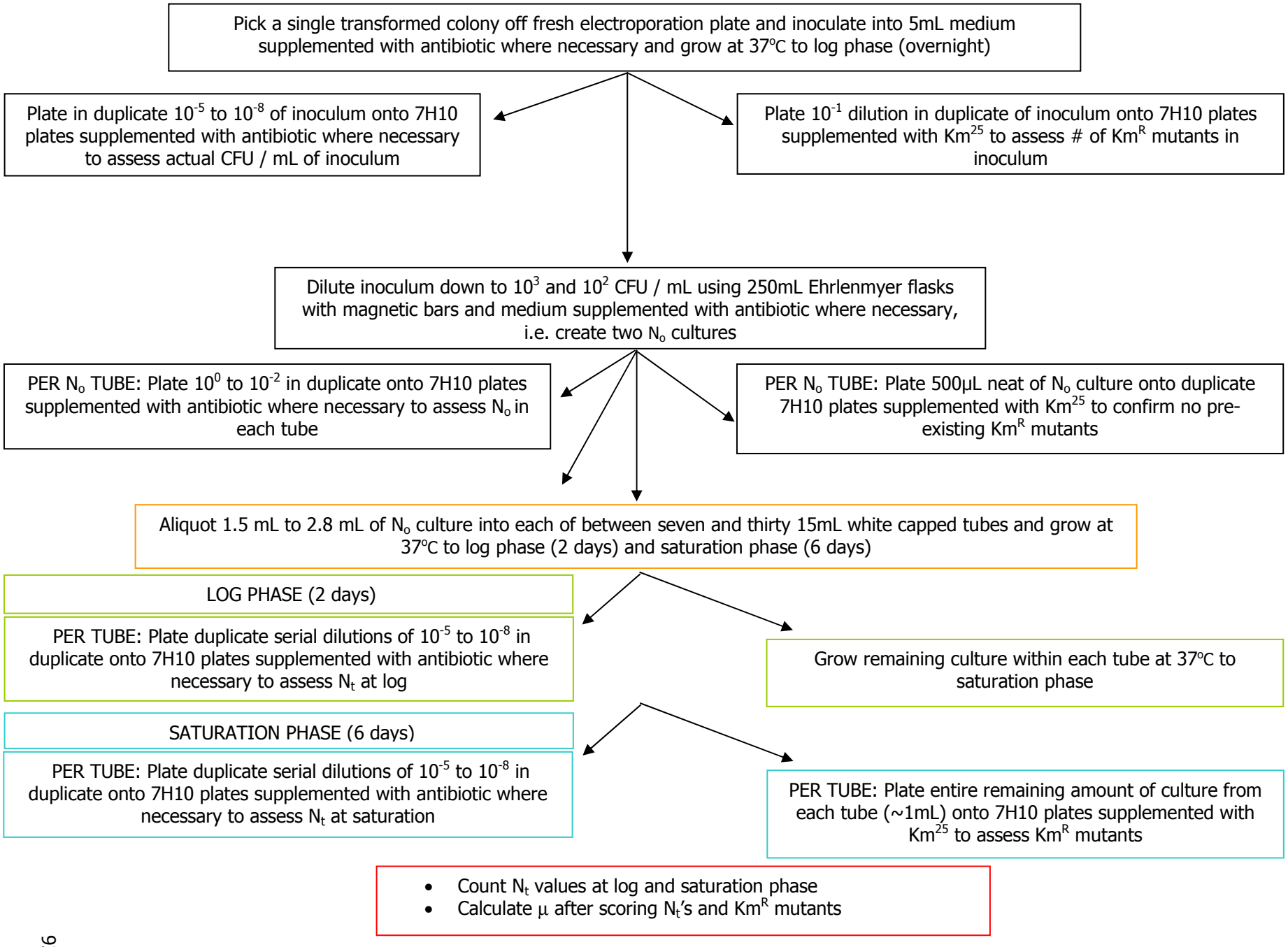
Appendix C : Specific experimental requirements for Fluctuation Tests used in this study

The principles of the Luria Delbrück Fluctuation Test remained the same for each experiment, but the individual experimental requirements differed and are set out Table C1. The flow diagram on page 2 of Appendix C illustrates the general protocol used for all Fluctuation Tests in this study. Changes to the protocol used with the mc^2 *his*G380E strain are detailed in Section 2.11.2.

Table C1: Specific experimental parameters used for each Fluctuation Test in this study

Strain	**Medium**	**Additional constituents**	**# N_t tubes assessed**
mc^2 155 (pGRAK)	LB	Gm^2	10
mc^2 155 (pGRAK)	2TY	Gm^2	10
mc^2 155 (pGRAK)	MADC-Tw 80	Gm^2	15
mc^2 155 ΔrecA (pGRAK)	MADC-Tw 80	Gm^2	7
mc^2 155 (pGRAK / pOLYGaa)	LB	Gm^2 and Hyg^{50}	30
mc^2 155 (pGRAK / pOLYGaa)	MADC-Tw 80	Gm^2 and Hyg^{50}	15
mc^2 155 (pGRAK / pOLYGaadinP)	MADC-Tw 80	Gm^2 and Hyg^{50}	15
mc^2 155 (pGRAK / pOLYGaadinX)	MADC-Tw 80	Gm^2 and Hyg^{50}	15
mc^2 155 ΔY (pGRAK)	MADC-Tw 80	Gm^2 and Hyg^{50}	14
mc^2 155 ΔL (pGRAK)	MADC-Tw 80	Gm^2 and Hyg^{50}	14
mc^2 155 (Rif resistance)	MADC-Tw 80	Rif^{150}	30
mc^2 155 *his*G380E	MADC-Tw 80	His^{100}	7

General Fluctuation Test protocol using *Mycobacterium smegmatis* mc^2 155



Appendix D : Techniques to limit clumping of mycobacterial cultures

To reduce the extent of clumping, culture tubes were placed in a beaker of water and secured with paper towel thereby creating a 'water jacket' in which the cultures were incubated (Figure D1A). This probably ensured even heat distribution to all culture tubes. Cultures that had clumped were mixed by aspiration with a 1 mL syringe needle. Furthermore, when assessing N_t values, all serial dilutions were made in 0.5% Tween 80. Combined, these three techniques proved effective in minimising the effects of clumping on N_t value determination (Figure D1B).

A

B

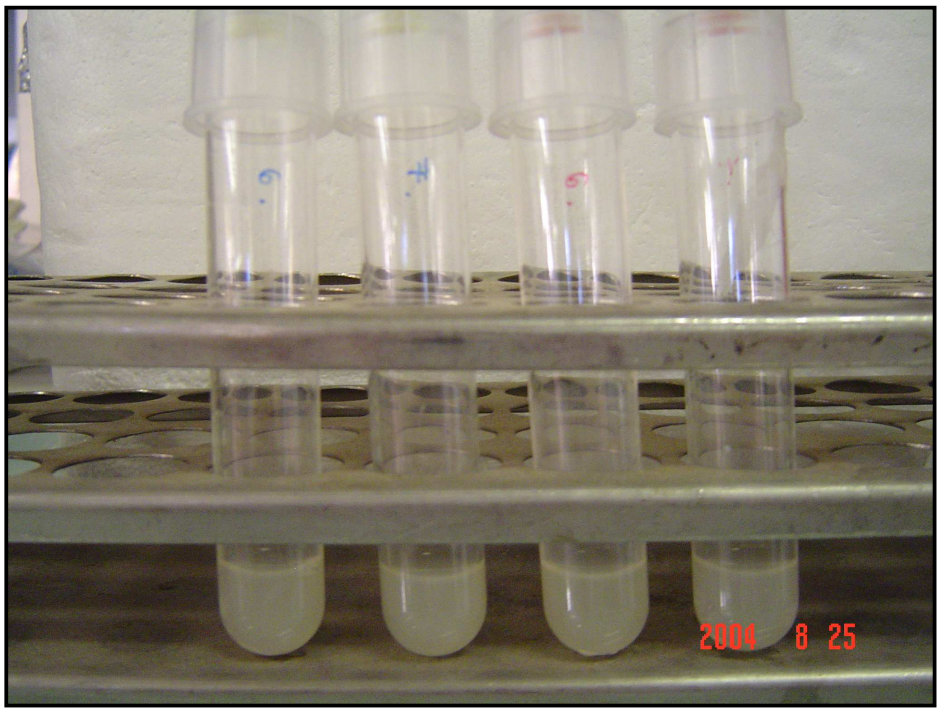


Figure D1: Clumping of mycobacterial cultures. (A) Culture tubes used in Fluctuation Tests were placed in a beaker partly filled with water and secured with paper towel. Cultures grown in this manner for 2 or 6 days (B) did not clump, therefore N_t values assessed from these tubes were reproducible.

Appendix E : Additional sequencing data from Morf2 region

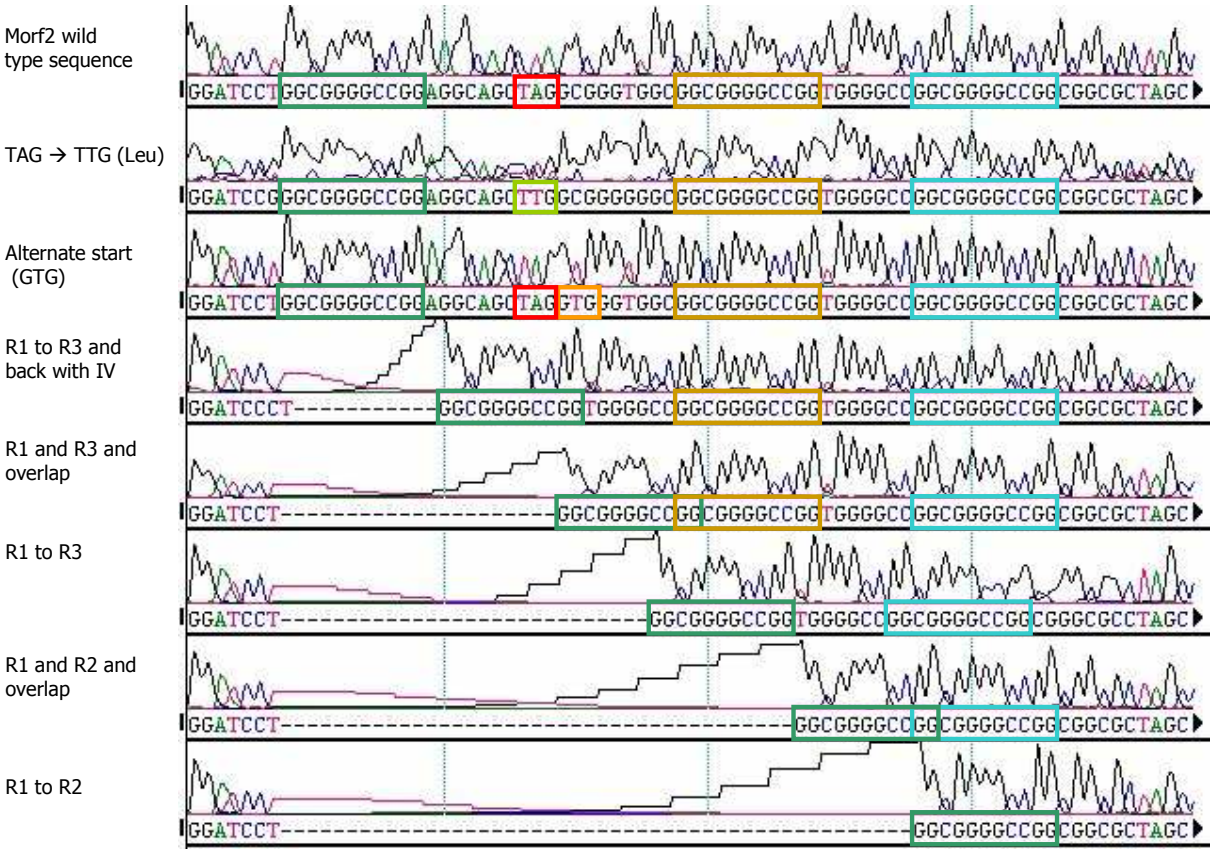


Figure E1: Sequence data of Morf2 region indicating a spectrum of mutations resulting in Km^R. G↓GATCC at the 5' end of the sequences indicates the *Bam*HI site at the start of the Morf2 region. G↓CTAGC at the 3' end of the sequence indicates the *Nhe*I site at the start of the 'aph cassette. R1 is highlighted by green blocks. The TAG stop codon is highlighted by red blocks. R2 and R3 are highlighted by blue and yellow blocks respectively. The point mutation within TAG to form a codon encoding Leucine is highlighted by the bright green block. The point mutation to form an alternative in frame start codon (GTG) is highlighted by the orange block. IV = intervening sequence.

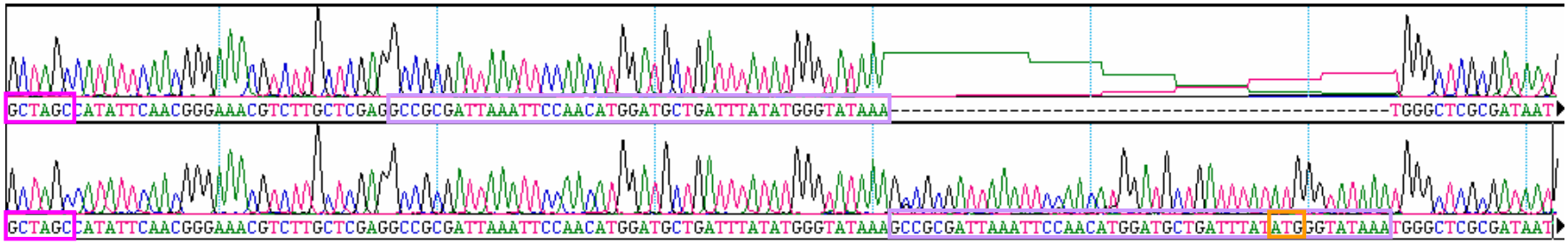


Figure E2: Sequence data indicating a Km^R clone with duplication in the 'aph cassette. The upper sequence indicates the wild type 'aph cassette from the *NheI* site at the 3' end of the Morf2 sequence (indicated by pink block at the 5' end of the sequence). The lower sequence indicates the Km^R mutant with the duplicated portion of the 'aph cassette (indicated by the purple blocks) that in turn created a new in frame ATG start codon (indicated by the orange block).

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