A model of RNA repair to study antibiotic tolerance

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***Abstract*— Antibiotic tolerance, the mechanism of bacteria transiently surviving antibiotic treatment, is emerging as a precursor to the development of full antibiotic resistance. An RNA repair system, the Rtc system, highly conserved across all domains of life, has recently been shown to promote antibiotic tolerance upon exposure to ribosome targeting antibiotics. The role of this system in the absence of antibiotics is largely unknown, and even less so the mechanisms by which tolerance is obtained. In this work, we develop and analyse a mathematical model to investigate the mechanistic action of Rtc leading to antibiotic tolerance in bacteria.**

I. Purpose

The Rtc system is an RNA repair system found in all domains of life, however little is known about its purpose. Recent work has highlighted the role of Rtc in maintaining RNA components of the translational apparatus, allowing bacteria to counteract the translation inhibiting effects of antibiotics, as well as roles in chemotaxis and motility processes [1]. The system consists of an RNA cyclase, RtcA, and an RNA ligase, RtcB, which together perform an end-healing and sealing function for RNA ends and are regulated by RtcR. Building a mathematical model of the Rtc system we investigate the potential of ribosome maintenance in rescuing growth upon antibiotic exposure.

II. Rtc model

The expression of *RtcA* and *RtcB* is tightly regulated by a σ^{54}-factor that requires an activator protein, RtcR. Under normal conditions RtcR exhibits negative self-autoregulation and requires cooperative activation by a ligand. Once active, RtcR interacts with the σ^{54}-RNA polymerase (RNAP) holoenzyme and using its ATPase activity, converts RNAP from the closed complex to the open complex, where transcription of RtcA and RtcB can begin [2].

We model expression of the three *Rtc* genes and their action on ribosomes. We further model ribosomes as three separate species (Fig. 1): healthy and damaged ribosomes, and 'healed' ribosomes that have been tagged by RtcA for 'sealing' by RtcB. Tagged ribosomes act as ligands to RtcR, and so a positive feedback loop is created, with tagged ribosomes leading to expression of RtcA and RtcB.

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A. Preliminary results

Preliminary analysis indicates a high sensitivity of *RtcAB* expression on ATP availability. The system further displays potential for bistability, which may explain the heterogeneity observed in the expression of *Rtc* and in tolerance levels across isogenic cells.

B. Future work

We will integrate the Rtc model with a mechanistic model of bacterial growth [3]. This will allow Rtc to be studied under various growth conditions, see how antibiotics affect its expression, and in turn, how Rtc effects bacterial growth.

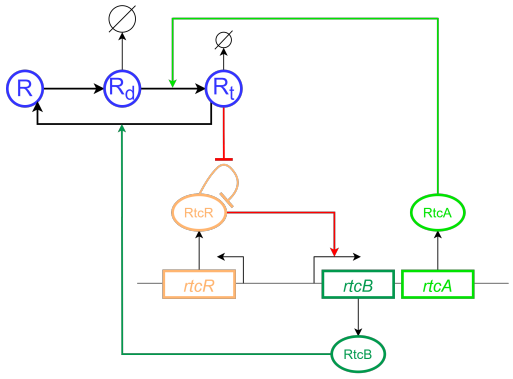

Fig. 1. **Model schematic of the Rtc system.** R represents healthy ribosomes, which are damaged by antibiotics to produce damaged ribosomes, R_d. Damaged ribosomes can be degraded or 'healed' by RtcA yielding tagged ribosomes R_t, which can then be 'sealed' back to healthy ribosomes by RtcB, or used as a ligand for RtcR activation. RtcA and RtcB are co-expressed from the same operon regulated by RtcR.

III. Conclusion

We propose the first mathematical model of the Rtc system for RNA repair, which promises to shed light on its role in antibiotic tolerance.

References

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