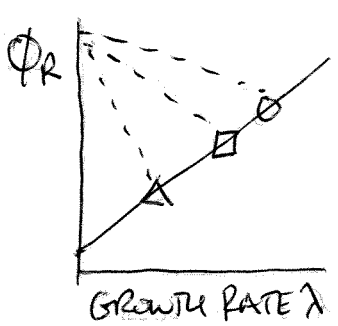
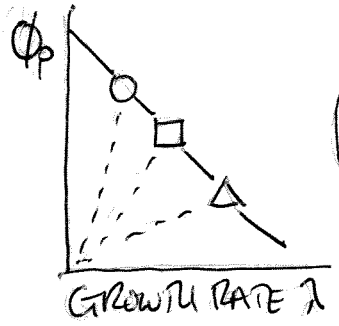
CONSEQUENCES OF THE PHENOMENOLOGICAL GROWTH MODEL

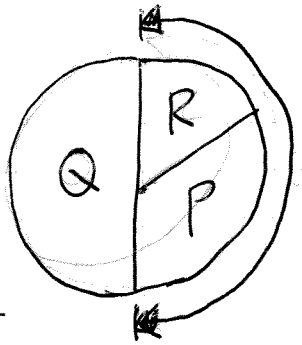
CONSEQUENCES:
- CONSTRAINTS ON GENE EXPRESSION
- CONSTRAINTS ON PHYSIOLOGICAL RESPONSE TO ANTIBIOTICS

"FORWARD PROBLEM"

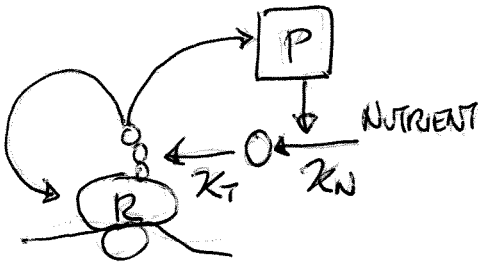
EMPIRICAL "GROWTH LAWS"





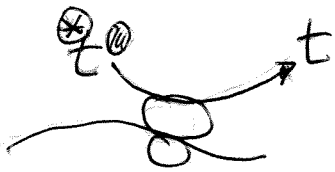


INTERPRETATION

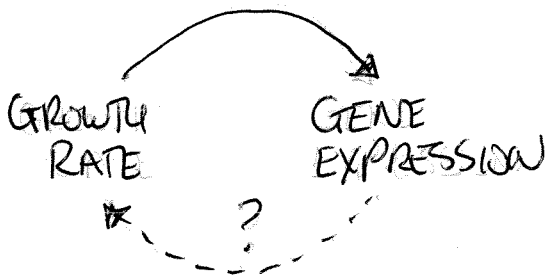


"INVERSE PROBLEM"

IMPLEMENTATION/ REGULATION



CONSTRAINTS ON GENE EXPRESSION

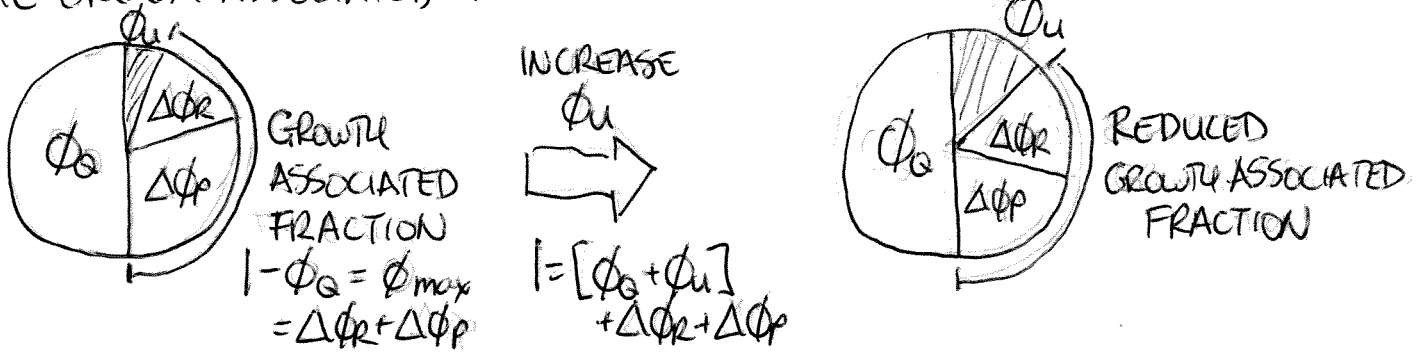


THE MAIN IDEA IS: GROWTH RATE AFFECTS GENE EXPRESSION.
WHAT ABOUT THE OTHER DIRECTION?
CAN GENE PRODUCTS AFFECT GROWTH RATE?
WILL THIS PRODUCE 'GROWTH MEDIATED' FEEDBACK LOOPS?

PROTEIN OVEREXPRESSION

BACTERIA IS OFTEN USED TO PRODUCE HIGH-VALUE BIOPRODUCTS – VALUABLE TO US (LIKE INSULIN), BUT PROVIDE NO BENEFIT TO THE BACTERIUM (FROM ITS POINT OF VIEW, THE PROTEIN IS 'USELESS')

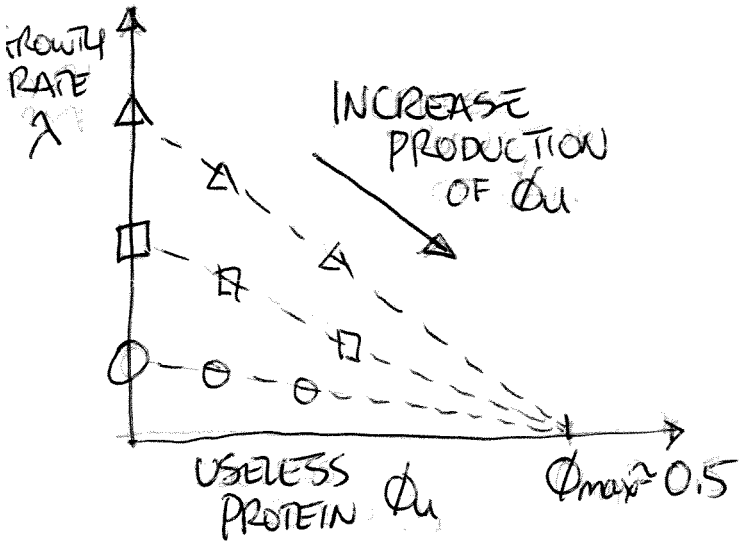
THE PROTEIN MASS FRACTION OF THE USELESS PROTEIN IS DENOTED ϕ_u – WHAT EFFECT WILL PROTEIN PRODUCTION HAVE ON GROWTH? FROM THE PROTEOME PARTITION, ϕ_u WILL INCREASE THE FIXED (NON-GROWTH ASSOCIATED) OVERHEAD ϕ_Q, THEREBY DECREASING THE GROWTH ASSOCIATED FRACTIONS:



FROM THE EMPIRICAL GROWTH LAWS:

$$\lambda = \gamma_T \Delta\phi_R = \gamma_N \Delta\phi_P$$

SO THE GROWTH RATE SHOULD DECREASE LINEARLY WITH ϕ_u.

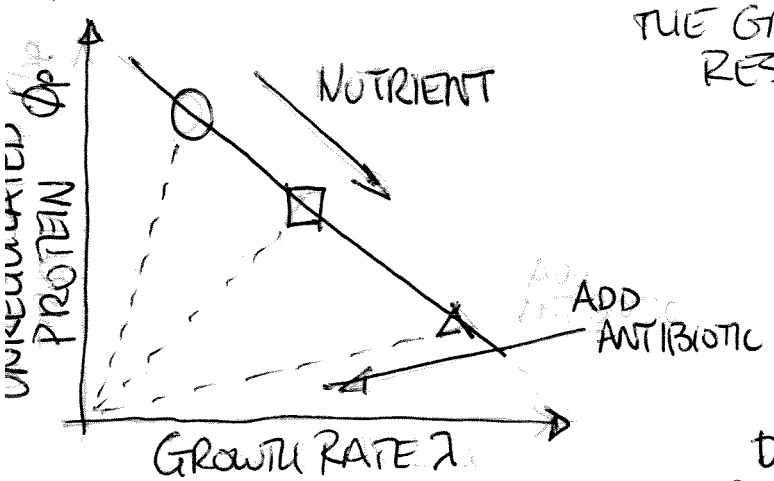


THIS IS A PURELY PASSIVE EFFECT – THE RESPONSE WILL OF COURSE BE MORE SEVERE IF THE USELESS PROTEIN IS ALSO TOXIC.

BUT AT THE LEAST, THERE WILL BE A LINEAR BURDEN

GROWTH MEDIATED FEEDBACK LOOPS

CHANGES IN GROWTH RATE CHANGE PROTEIN LEVELS, EVEN UNREGULATED PROTEINS. WHAT IF ONE OF THOSE UNREGULATED PROTEINS CHANGES THE GROWTH RATE eg. ANTIBIOTIC RESISTANCE?



DEPENDING UPON THE LOGIC OF THE CONNECTION, CAN GENERATE FEEDBACK LOOPS THAT ARE NOT ENCODED DIRECTLY IN THE GENOME!

CONSIDER A RIBOSOME-TARGETING ANTIBIOTIC -

MECHANISM OF ACTION

MECHANISM OF RESISTANCE

IN THE ABSTRACT, ANTIBIOTIC RESISTANCE GIVES RISE TO THE FOLLOWING INTERACTION MAP:

$$\lambda = \frac{\phi_{max}}{1/\kappa_T + 1/\kappa_N}$$

GROWTH RATE λ ← POSITIVE INTERACTION ← TRANSLATION RATE κ_T

$X = \beta \cdot \lambda$ — INDIRECT REGULATION

UNREGULATED RESISTANCE PROTEIN X

NEGATIVE INTERACTION

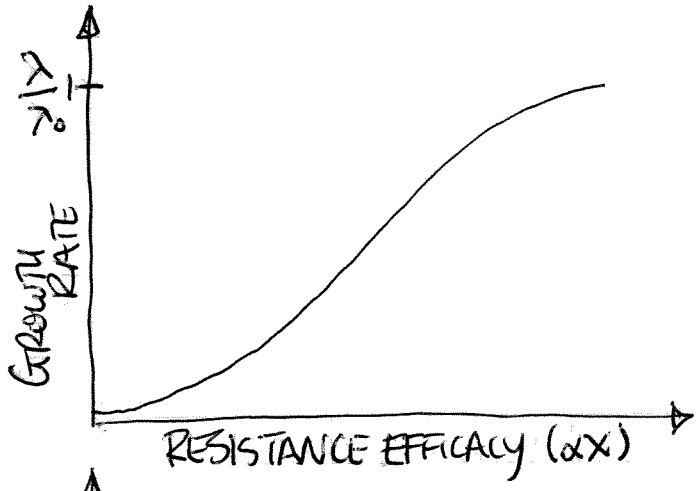
INTRACELLULAR ANTIBIOTIC A_{in} ★

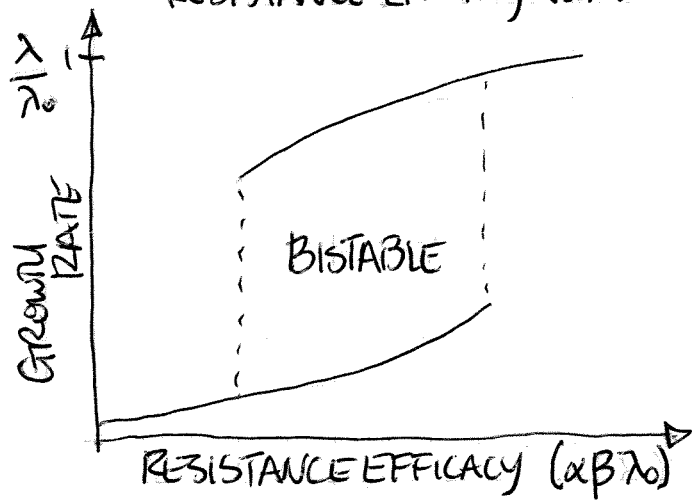
NEGATIVE INTERACTION

eg $\kappa_T = \frac{\kappa_T^{max}}{1 + A_{in}}$

eg $A_{in} = \frac{A_{out}}{1 + (\alpha X)^2}$

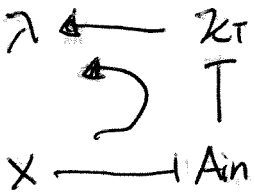
PHENOTYPE





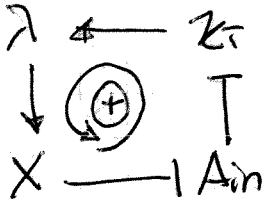
GENOTYPE

OPEN LOOP



SLOPE IS IMPORTANT INDICATOR OF RESISTANCE 'PAYOFF'

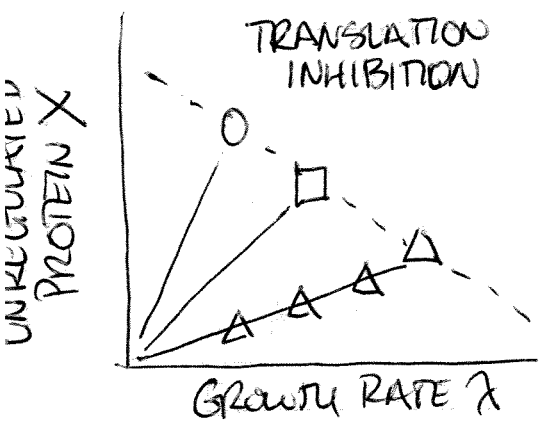
CLOSED LOOP

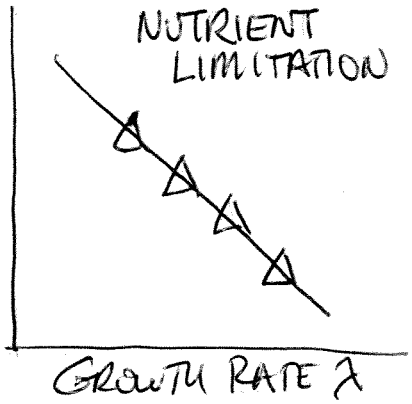


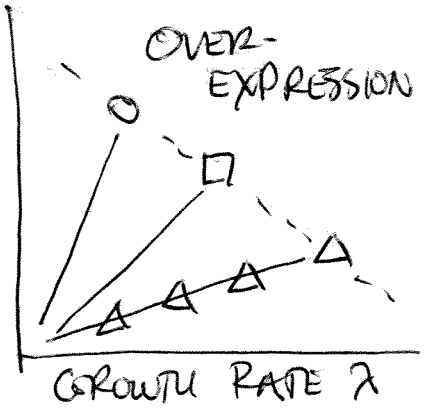
CLOSED LOOP EXHIBITS POSITIVE FEEDBACK eg MICROPHONE POINTED AT SPEAKER

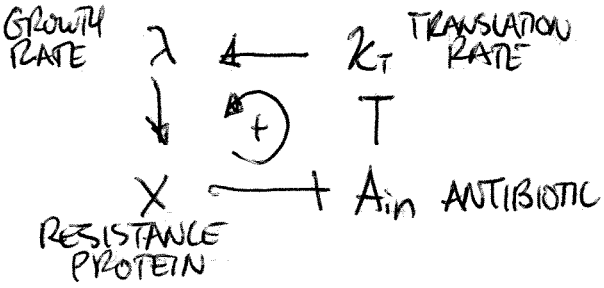
POTENTIALLY BISTABLE, CERTAINLY VERY SENSITIVE.

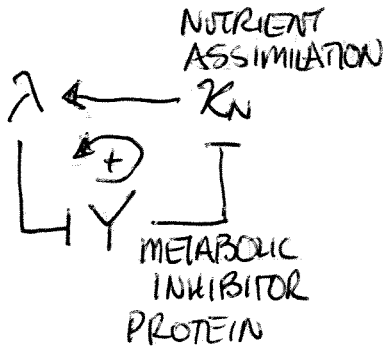
THIS TYPE OF ANALYSIS CAN BE EXTENDED TO OTHER SCENARIOS:

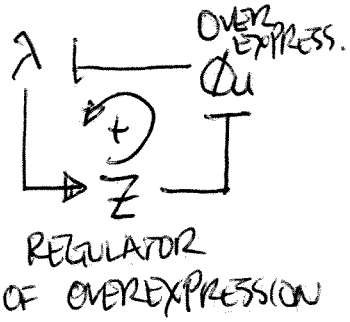












ANTIBIOTIC RESISTANCE

BACTERIAL PERSISTENCE

VIRULENCE? FLAGELLA? BIOPRODUCTION?

⊛ CAN WE DESIGN ANTIBIOTIC COMBINATIONS TO FRUSTRATE THIS TYPE OF RESISTANCE AQUISITION?

⊛ CAN WE DESIGN BIOPRODUCTION VECTORS THAT ARE NOT SUBJECT TO PARASITIC OVERGROWTH?