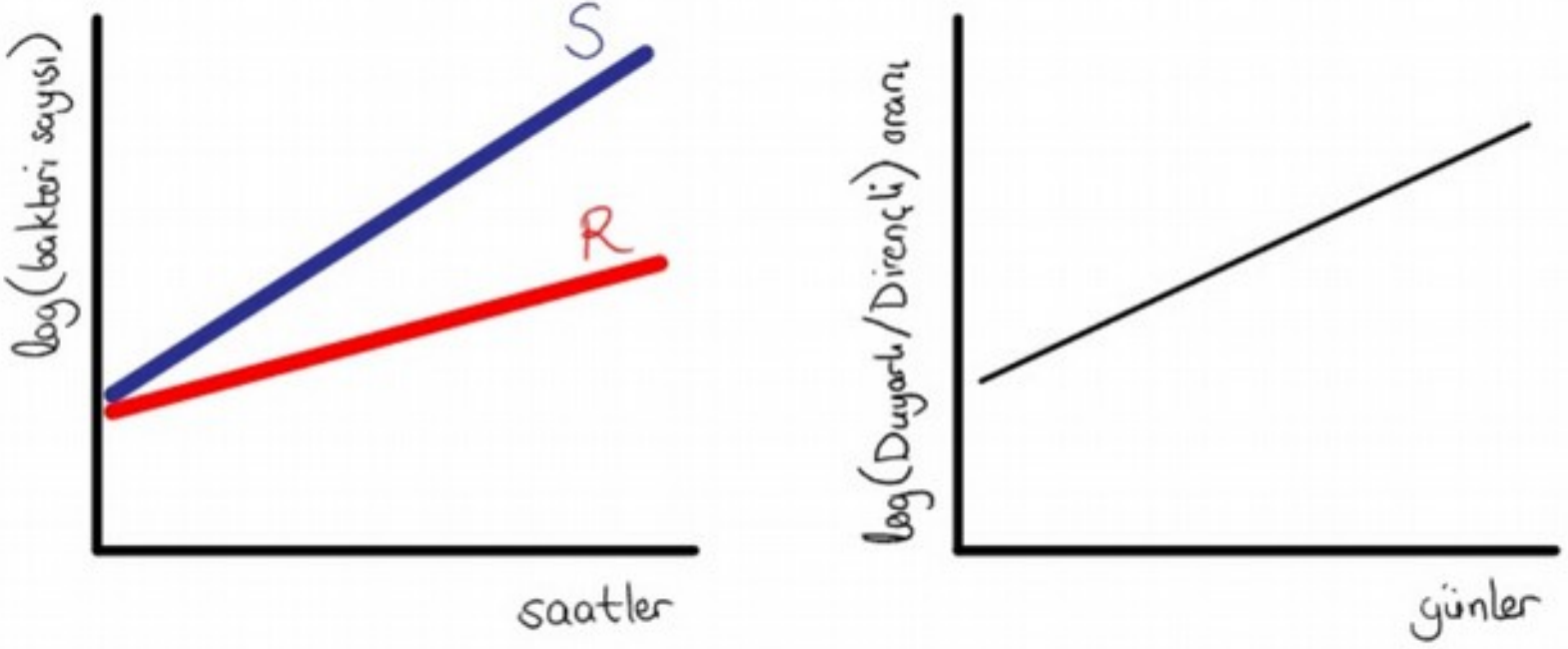
Mikrobiyal stres ve üretim süreçlerindeki rolü

Antimikrobiyallerin altın çağı

Sömürülen mucize

Antibiyotik "işi" eskisi kadar karlı değil...

"FITNESS" nedir ve nasıl ölçülür?

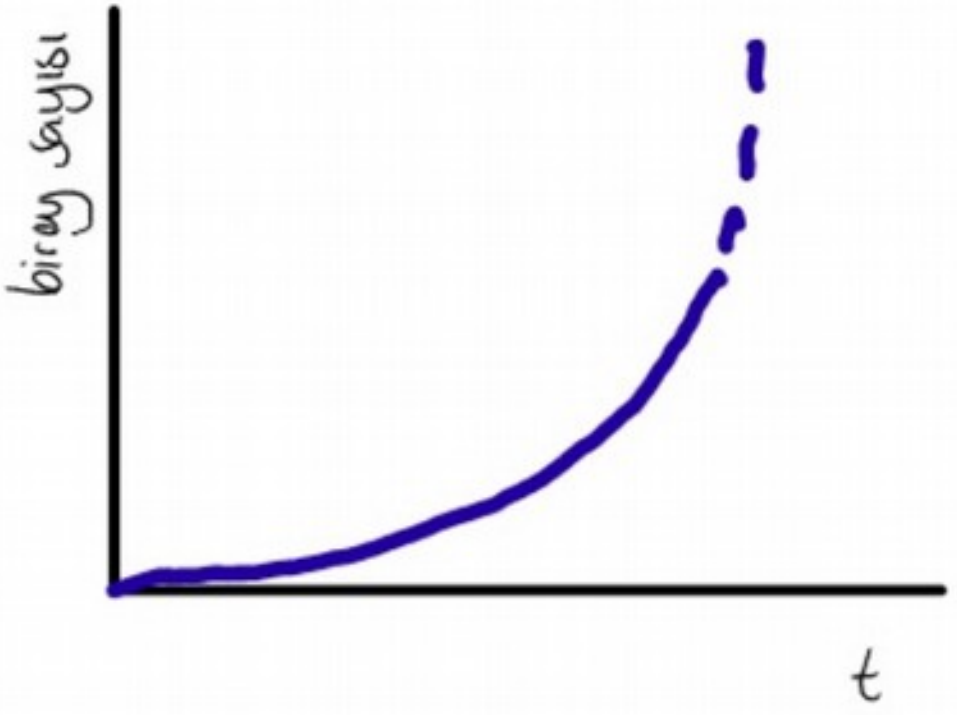


Duyarlı ve Dirençli hücreler arasında "fitness" farkı...

in vitro ve *in vivo* ölçülmeli

Antimikrobiyal etkisi altında olmayan hücrelerde üremenin kinetiği bir şeyler anlatıyor

Temelde, bakteri üremesinin modeline gereksinimimiz var:



$$\frac{dx}{dt} = kx$$

$$\Rightarrow \frac{dx}{x} = k\,dt$$

$$\Rightarrow \int_{x(0)}^{x(t)} \frac{dx}{x} = k \int_{0}^{t} dt$$

$$\Rightarrow \ln \frac{x(t)}{x(0)} = kt$$

$$\Rightarrow \boxed{x(t) = x(0)\, e^{kt}}$$

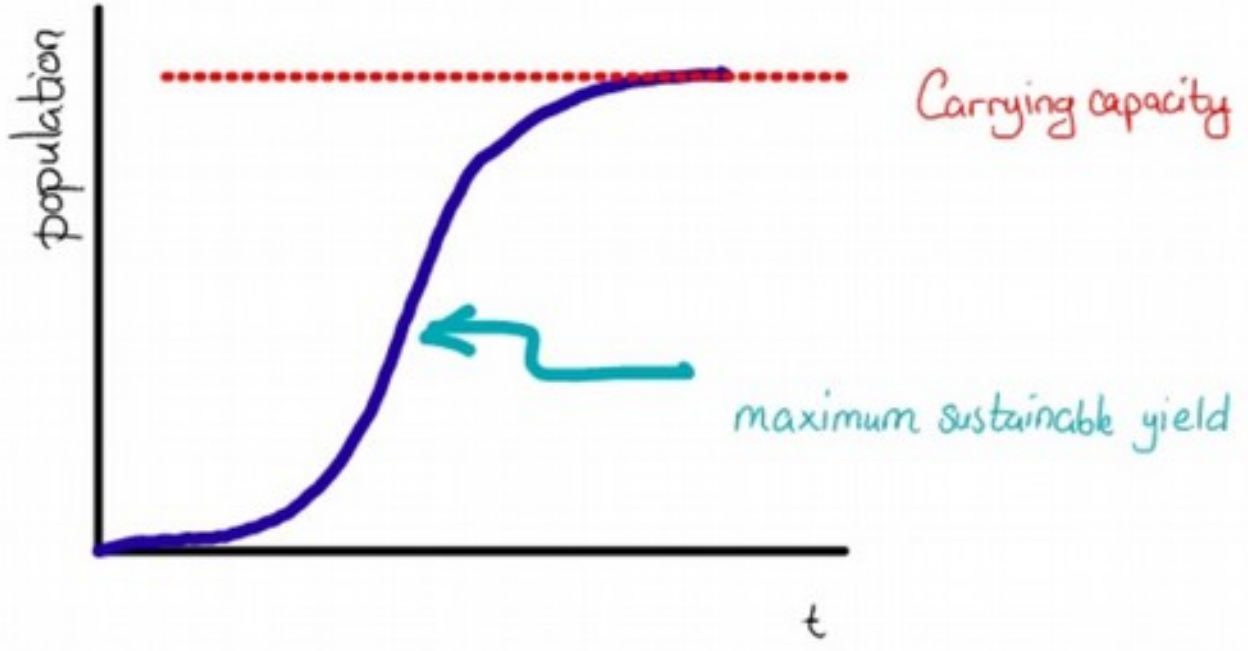
Daha makul bir yaklaşım:

density dependence of growth rate

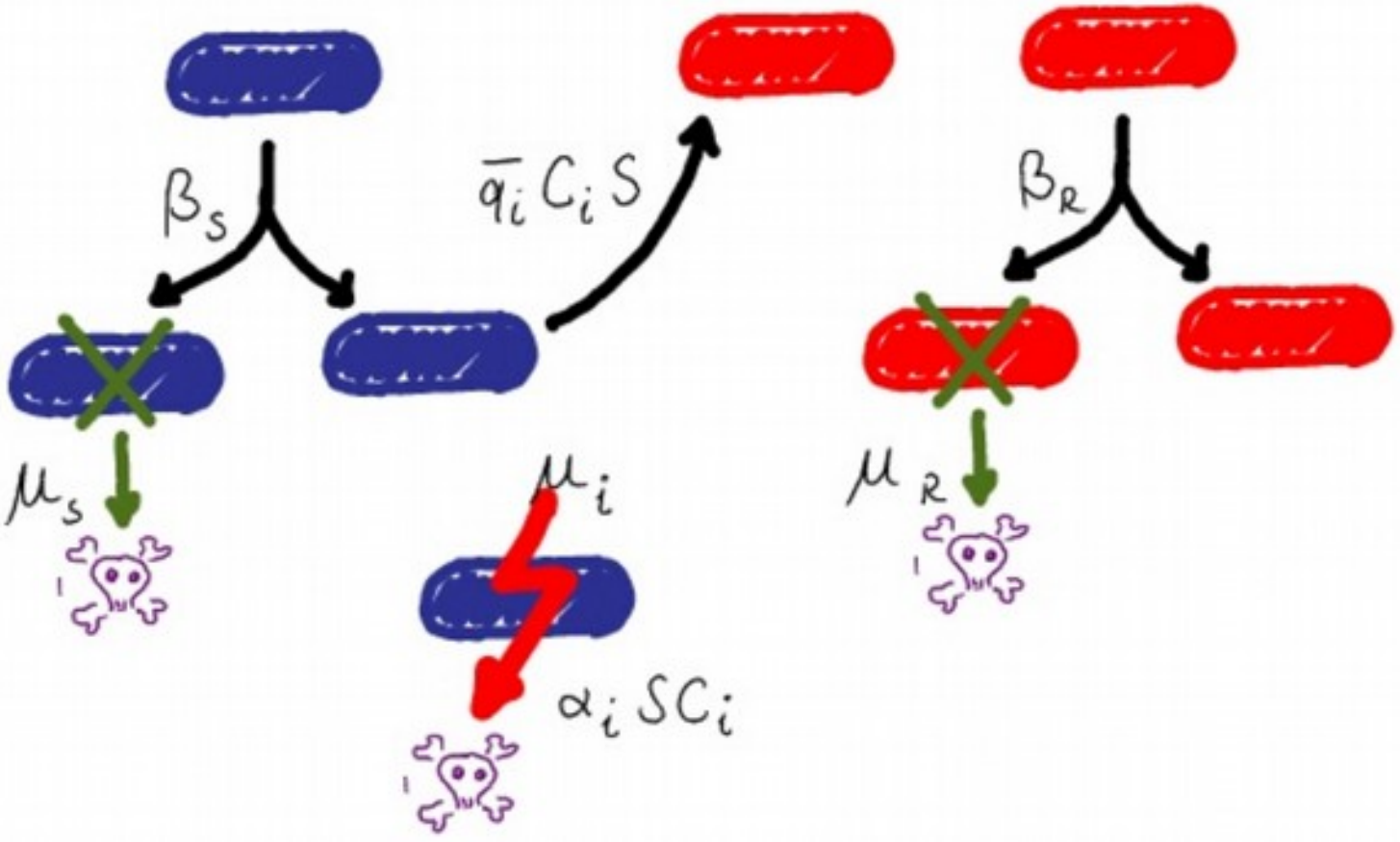
$$\frac{dP}{dt} = rP\left(1 - \frac{P}{K}\right)$$

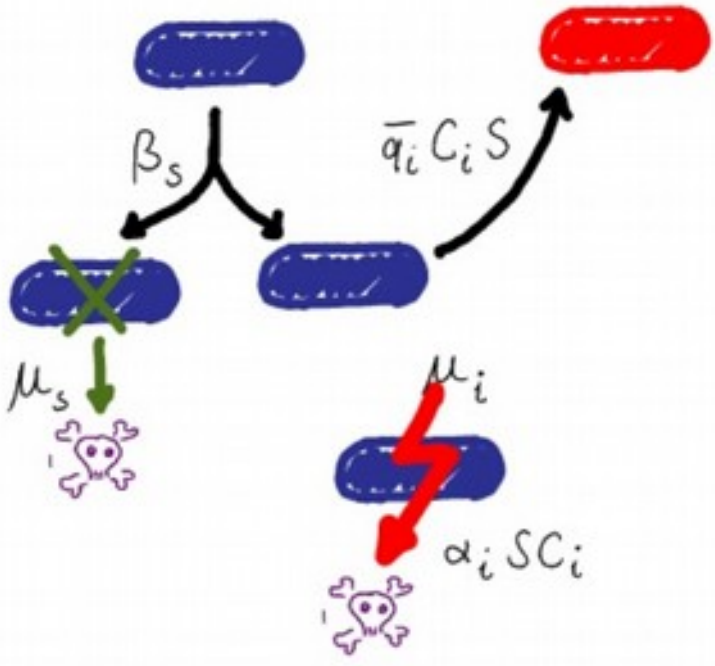
rate of growth when $N \ll K$

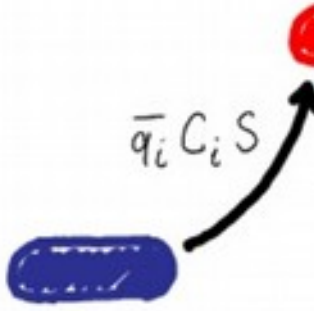
Populations increase towards a stable level: Carrying capacity



Antimikrobiyale maruziyet sırasında:







$$\frac{dR}{dt} = \beta_r R\left(1 - \frac{}{}\right.$$

$$\frac{dS}{dt} = \beta_s S\left(1 - \frac{S+R}{K}\right) - \sum_{i=1}^{n} (\bar{q}_i + \bar{\alpha}_i) C_i S - \mu_s S$$

r_s $\quad S \to R$ $\quad S \to$ $\quad$ antibiotic

$$\beta_r R\left(1 - \frac{S}{}\right.$$

$$\frac{dS}{dt} = \beta_s S\left(1 - \frac{S+R}{K}\right) - \sum_{i=1}^{n} (\bar{q}_i + \bar{\alpha}_i) C_i S - \mu_s S$$

r_s — $S \to R$ — $S \to$  — 

antibiotic

$$\beta_s S\left(1 - \frac{S+R}{K}\right) = \mu_s S + \sum_{i=1}^{n} (\bar{q}_i + \bar{\alpha}_i) C_i S$$

$$S_v = \frac{\beta_s}{\sum_{i=1}^{n} (q_i + \alpha_i) + \mu_s}$$

average number of bacteria generated by the S fraction, that survives the effects of antibiotics & mutation

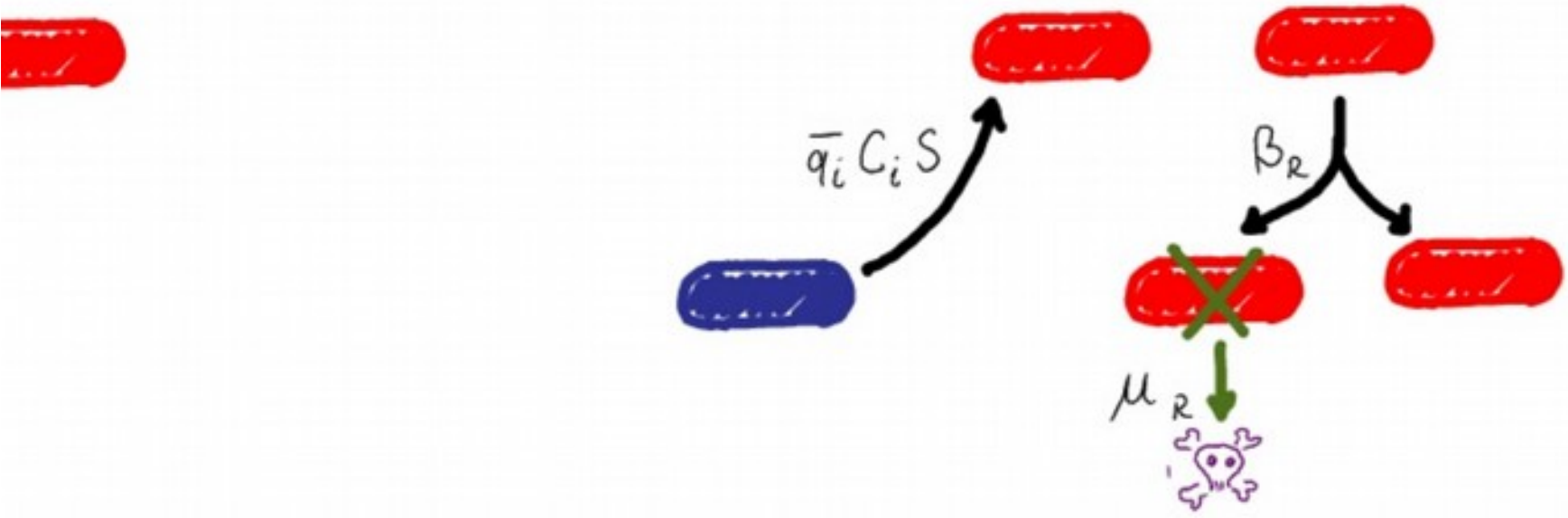
$$\beta_r R\left(1 - \frac{S}{K}\right)$$

R_r

averag

generat

	Resistance in compensated mutant
	Maintained
	Maintained



$$\frac{dR}{dt} = \beta_r R\left(1 - \frac{S+R}{K}\right) + \sum_{i=1}^{n} \bar{q}_i C_i S - \mu_r R$$

$S \rightarrow R$

$\bar{q}_i C_i S - \mu_s S$

$$\frac{dR}{dt} = \beta_r R\left(1 - \frac{S+R}{K}\right) + \sum_{i=1}^{\hat{n}} \bar{q}_i C_i S - \mu_r R$$

$S \to R$

$- \mu_s S$

$\beta_r R\left(1 - \frac{S+R}{K}\right) = \mu_r R - \sum_{i=1}^{\hat{n}} \bar{q}_i C_i S$

$$R_r = \frac{\beta_r}{\mu_r}$$

average number of progeny generated by R bacteria

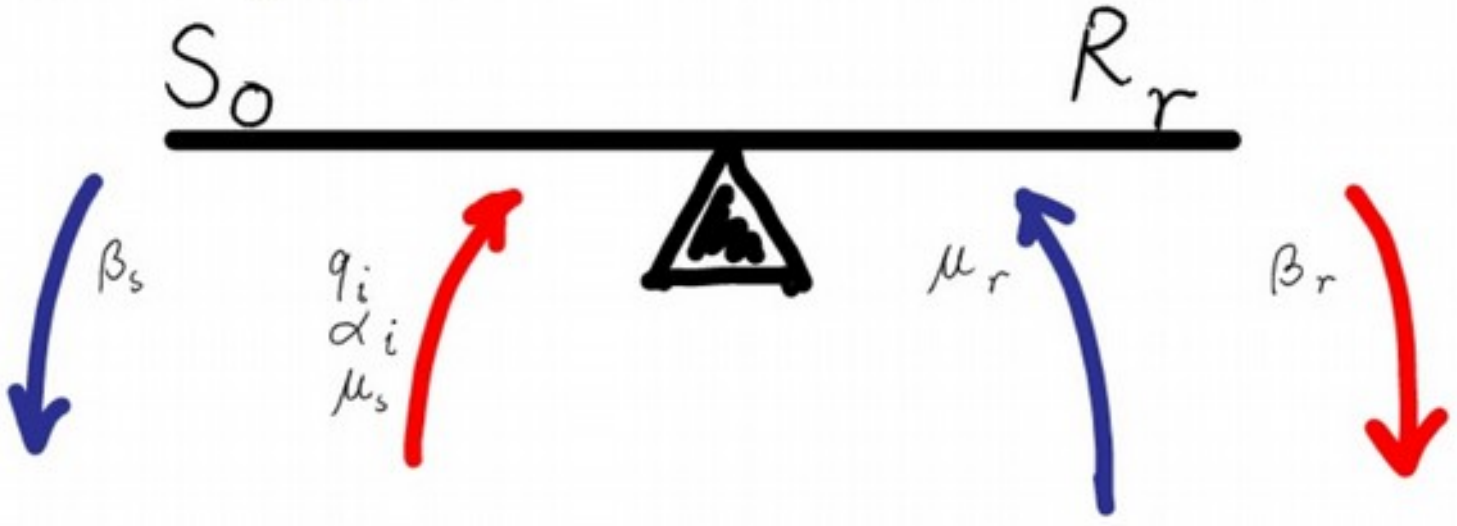
$(\bar{q}_i + \bar{\alpha}_i) C_i S$

$$S_o = \frac{\beta_s}{\sum_{i=1}^{n} (q_i + \alpha_i) + \mu_s}$$

average number of bacteria generated by the S fraction, that survives the effects of antibiotics & mutation

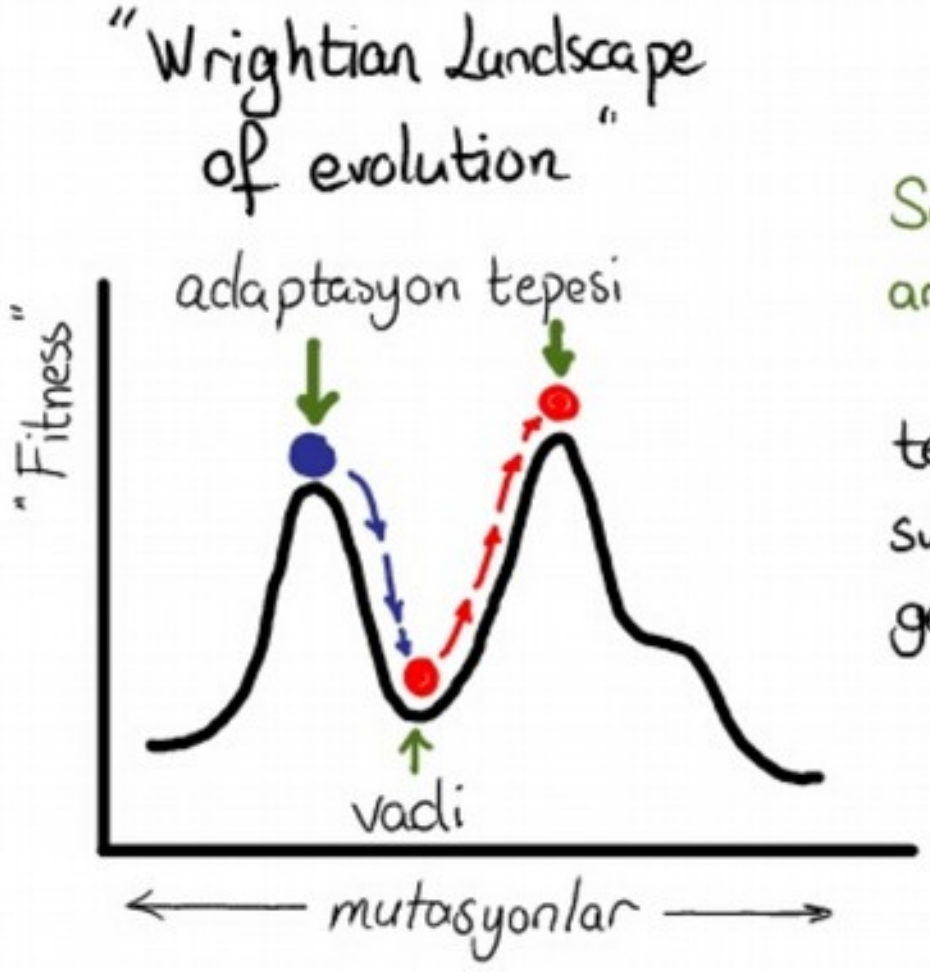
$$R_r = \frac{\beta_r}{\mu_r}$$

average number of progeny generated by R bacteria



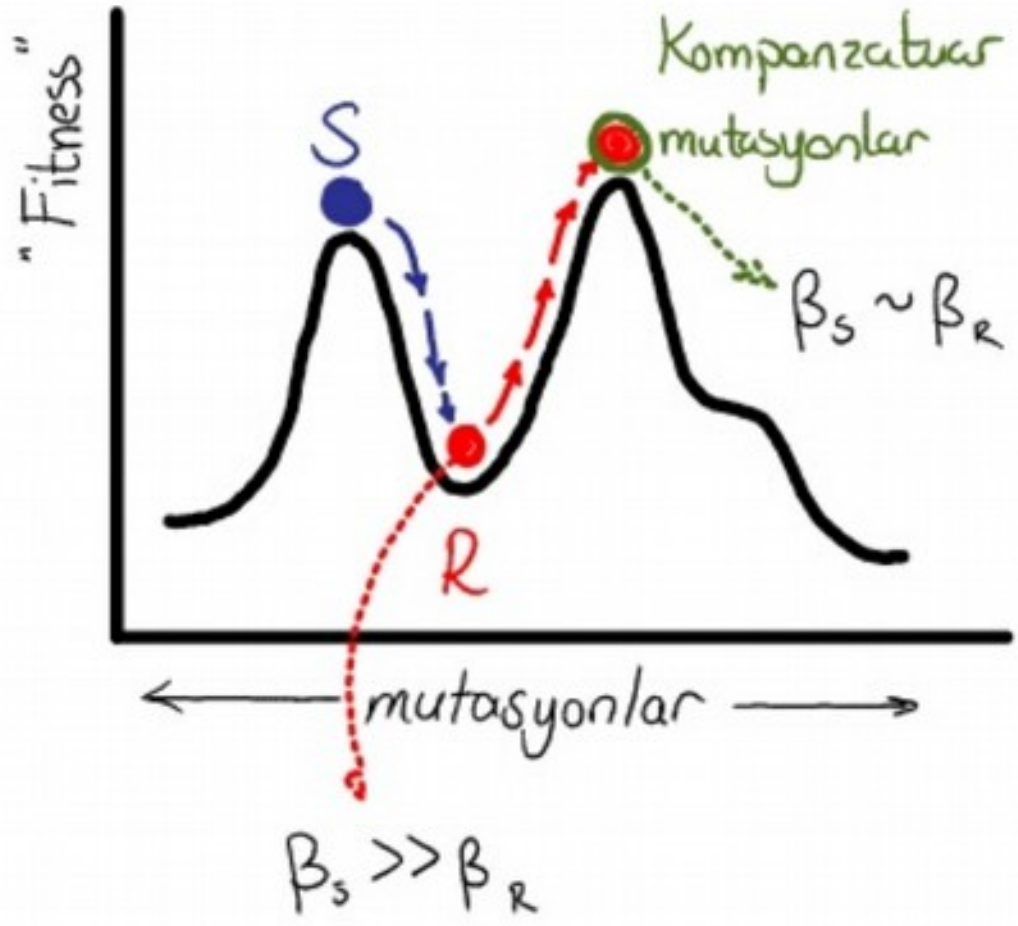
FITNESS

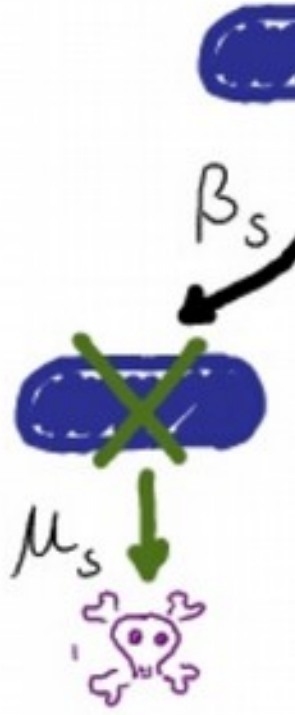
Stres her yerde ve her zaman...
Mikroorganizmalar "milyar yıllık" deneyimlerini nasıl kazanıyor?

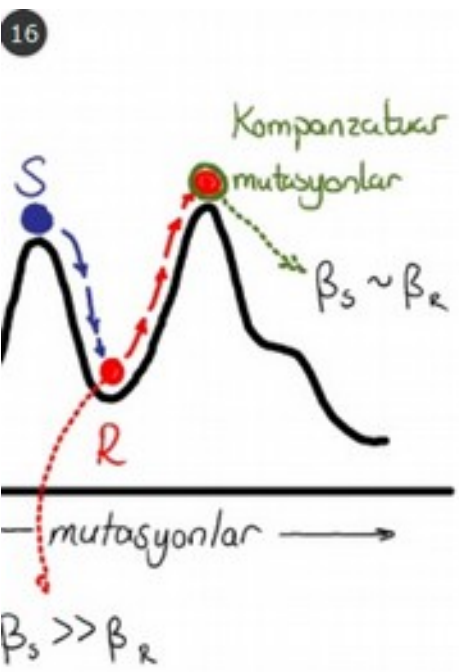


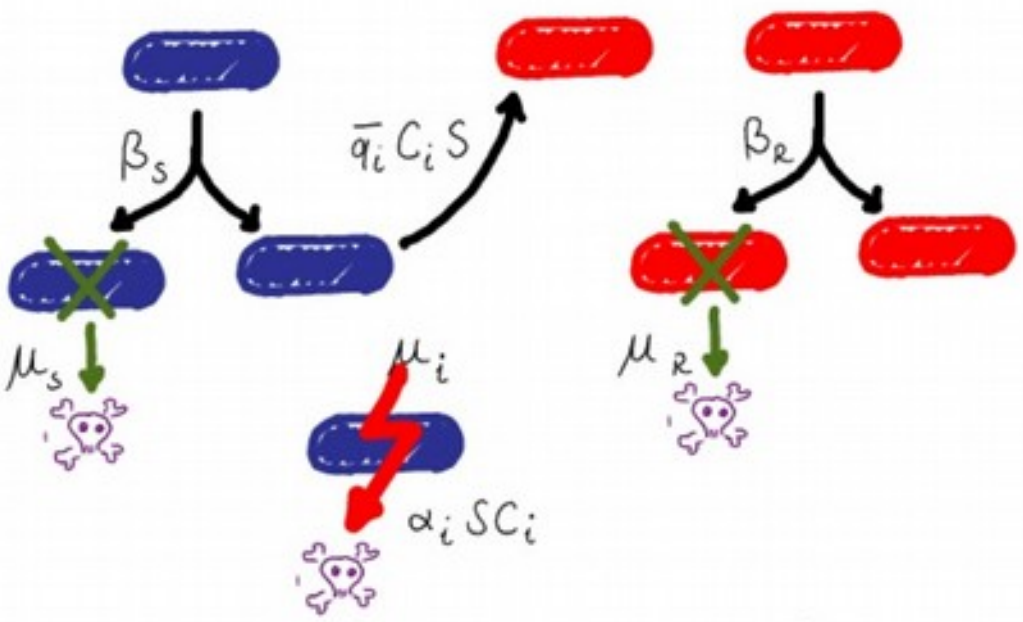
Salt doğal seçilim, "fitness" in sürekli artmasını gerektirmekte...

tepeden vadiye iniş için küçük subpopülasyonların GENETİK DRİFT geçirmesi: Shifting Balance Theory


"Fitness"
S
R
Kompanzatuar
mutasyonlar
$\beta_S \sim \beta_R$
mutasyonlar
$\beta_S >> \beta_R$


β_S
μ_S


Kompanzatuar
mutasyonlar
S
R
$\beta_s \sim \beta_R$
mutasyonlar
$\beta_s >> \beta_R$


β_s
$\bar{q}_i C_i S$
β_R
μ_s
μ_i
μ_R
$\alpha_i S C_i$


S_o
R_r
β_s
q_i
α_i
μ_s
μ_r
β_r
FITNESS

Escherichia coli $pTet^R$ için seleksiyon katsayısı = 0,007

Üreme hızında % 0,7 azalma

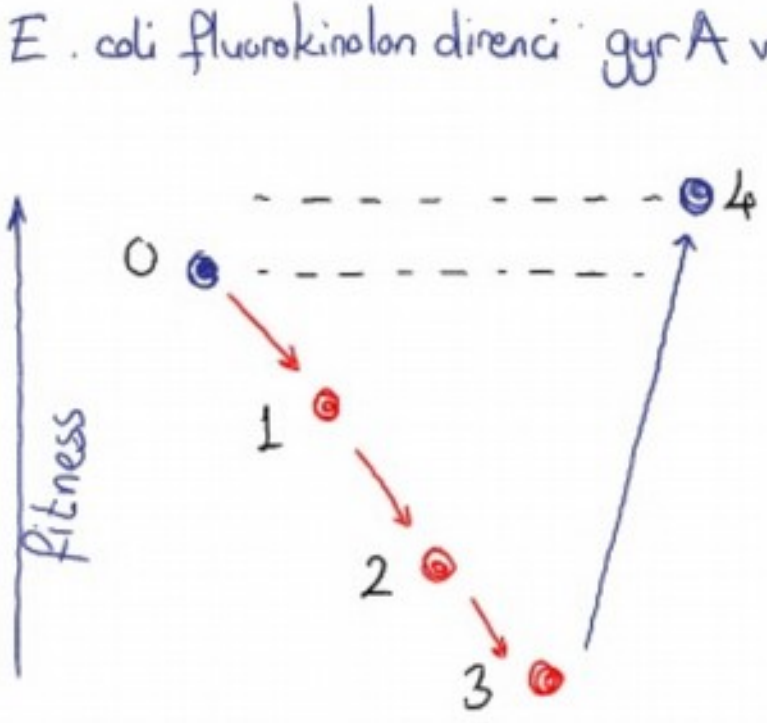
Direnç genini taşıyan plazmidin kaybedilmesi ile

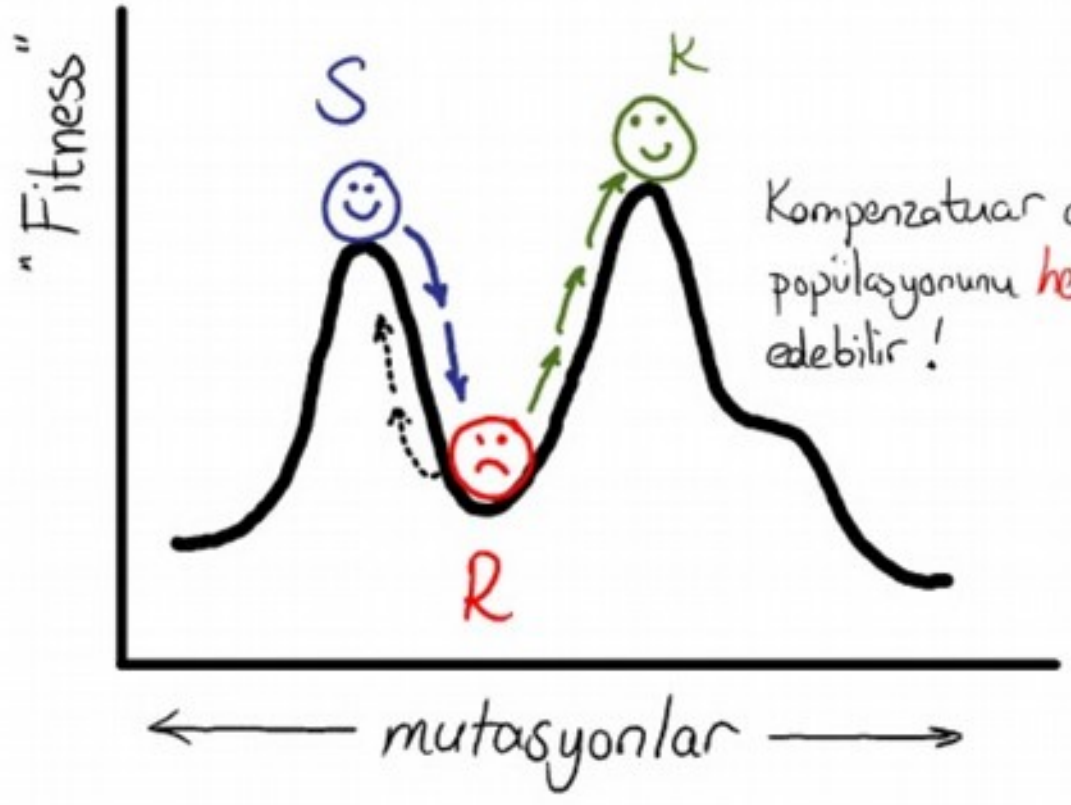
% 0,1 R : % 99,9 S hücre oranlarına dönebilmek için ~ 1.5 yıl süre gerekli!

5 haftada aynı dönüşüm için seleksiyon katsayısı ≥ 0.06 olmalı

22

Marcusson, L. L., Frimodt-Moller, N. & Hughes, D.Interplay in the selection of fluoroquinolone resistance and bacterial fitness. PLoS Pathog.5, e1000541 (2009).





Kompenzatuar evrim, bakteri popülasyonunu hemen stabilize edebilir!

☹ ⇒ ☺ geriye dönüş azımsanmayacak sayıda antimikrobiyal-bakteri çifti için imkansız değil, ancak YAVAŞ

Bonnie B

Lum

Syst
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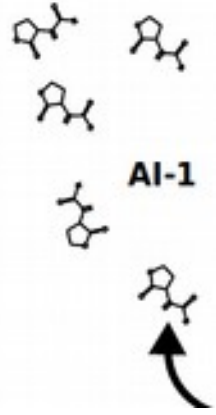
homos



? Azalmış virülans

? Azalmış bulaşıcılık

Biyolojik ve Epidemiyolojik Modeller Nasıl Yardımcı Olabilir?

Elde bulunan antimikrobiyellerin rasyonel kullanımına katkı

Kullanıma yeni girenlerin "korunması"

Alternatif yaklaşımla???

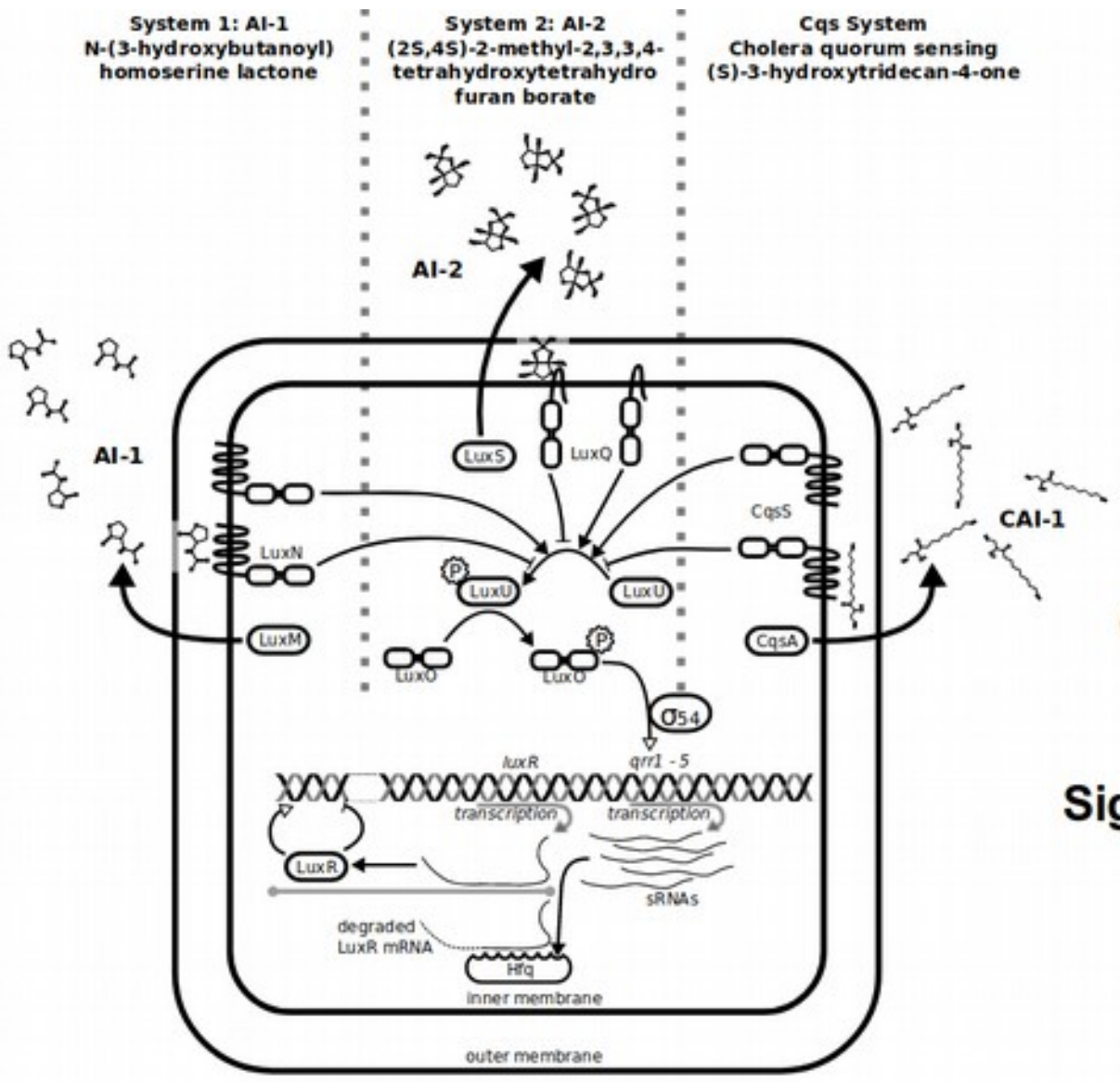
Alternatif hedefler:

Bakterilerin stres algısını düzenlemek

Hala çelişkili veriler bulunmaktu :

Krašovec et al.:
E. coli 'de rifampisin direncine neden olan mutasyon hızı plastisitesi "Quorum Sensing" ile ilişkili
↓ hücre yoğunlukları ⟶ ↑ mutasyon hızı
△ LuxS state ⟶ ↑ mutasyon hızı

Yalınkılıç & Engin:
E. coli 'de florokinolon direncinden sorumlu mutasyonların kazanılmasında QS rol oynuyor



Synthesis of the signal molecule

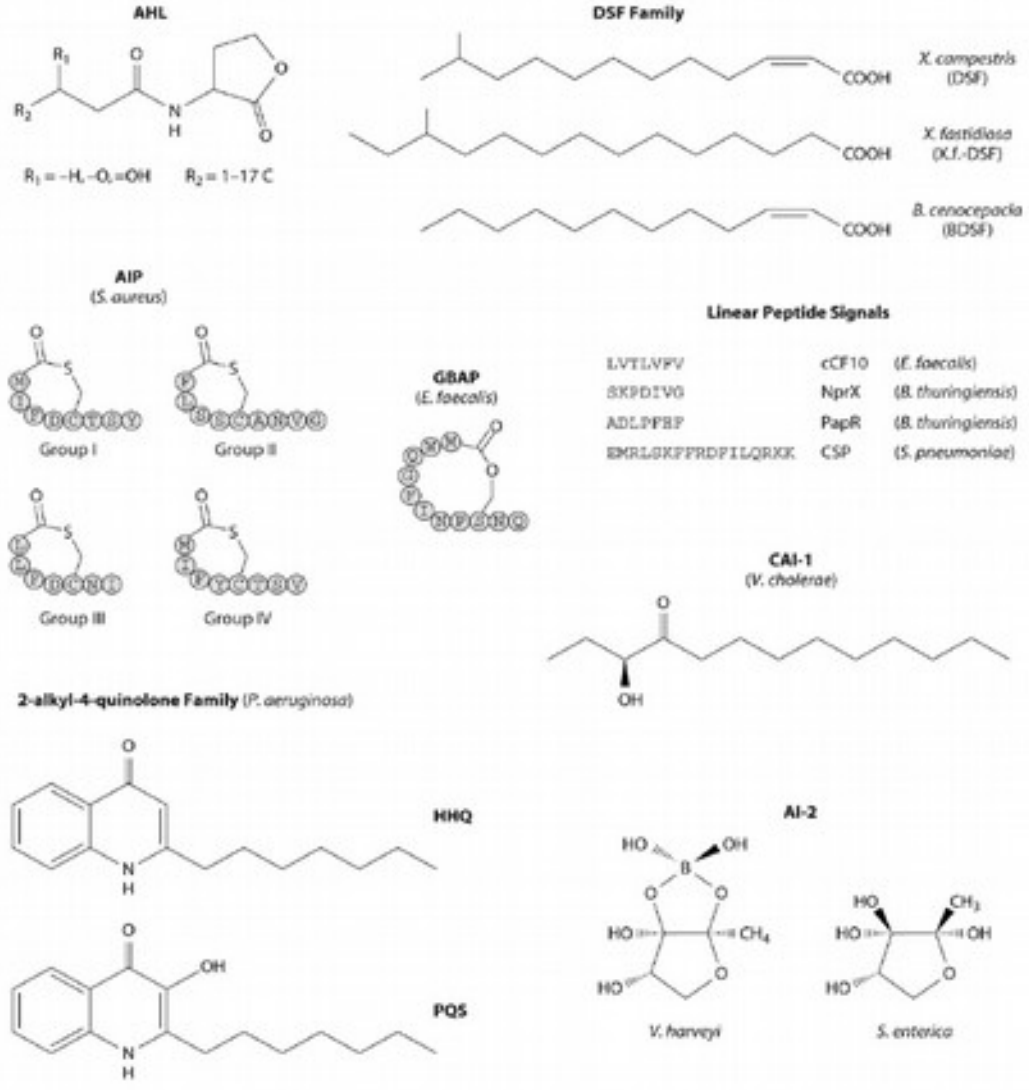
Liberation

Capturing by the receptor

Signal transduction & integration

Classes of autoinducers

(not an exhaustive list)



LaSarre B, Federle MJ. Exploiting Quorum Sensing To Confuse Bacterial Pathogens. Microbiol Mol Biol Rev. 2013 Mar 1;77(1):73–111.

29 cid-resistant
3–107 (2000)

→

ure

the selection
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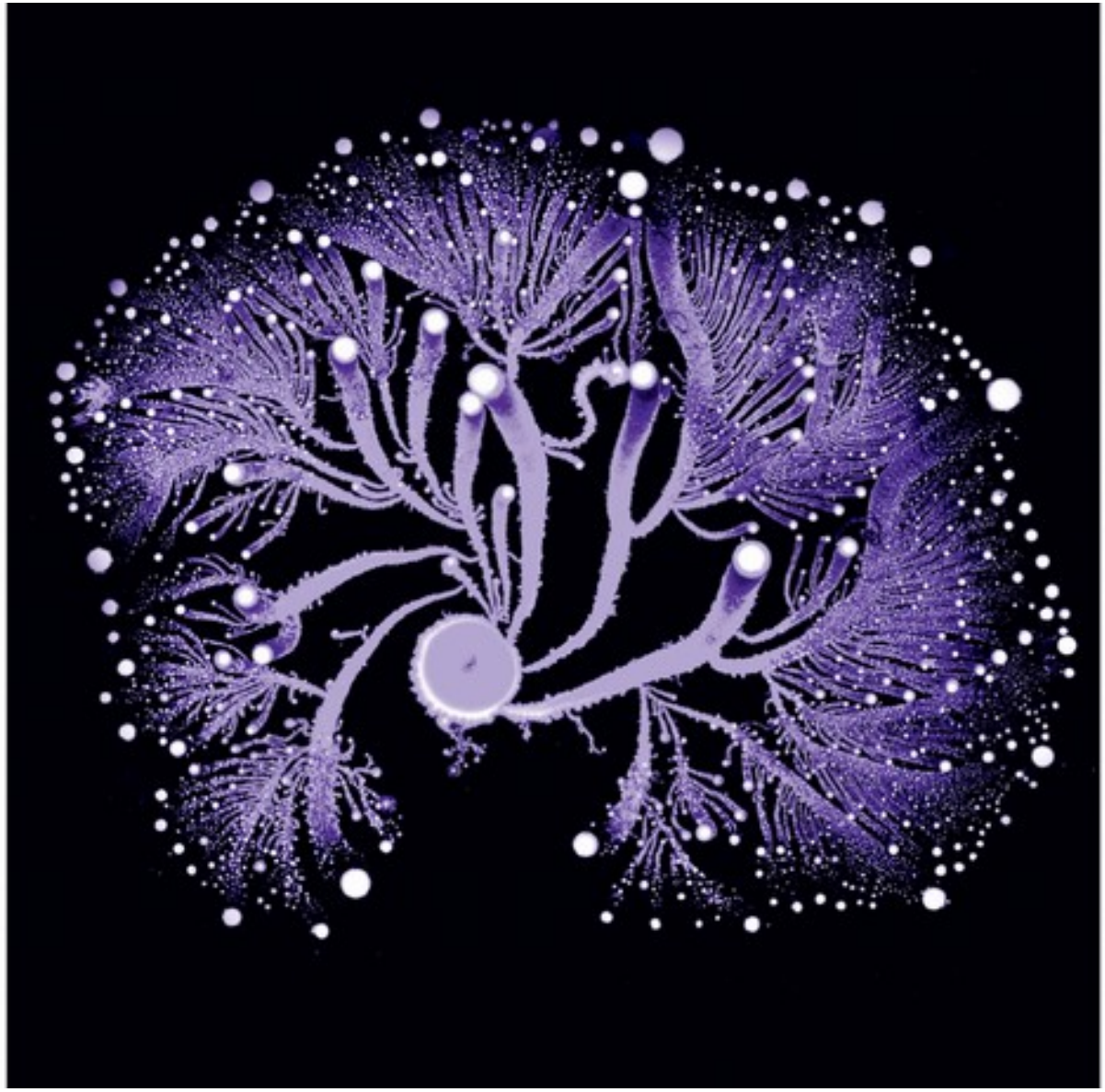
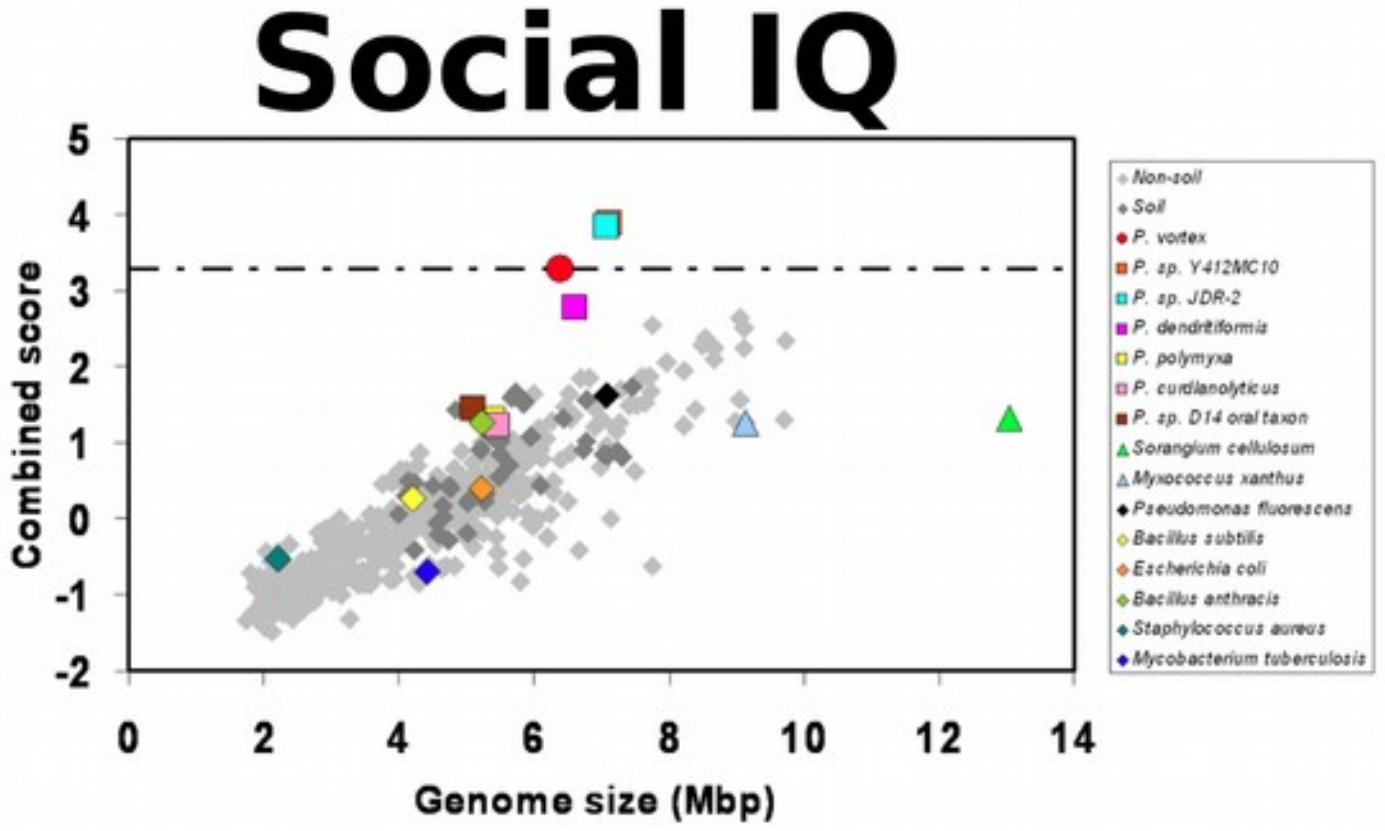
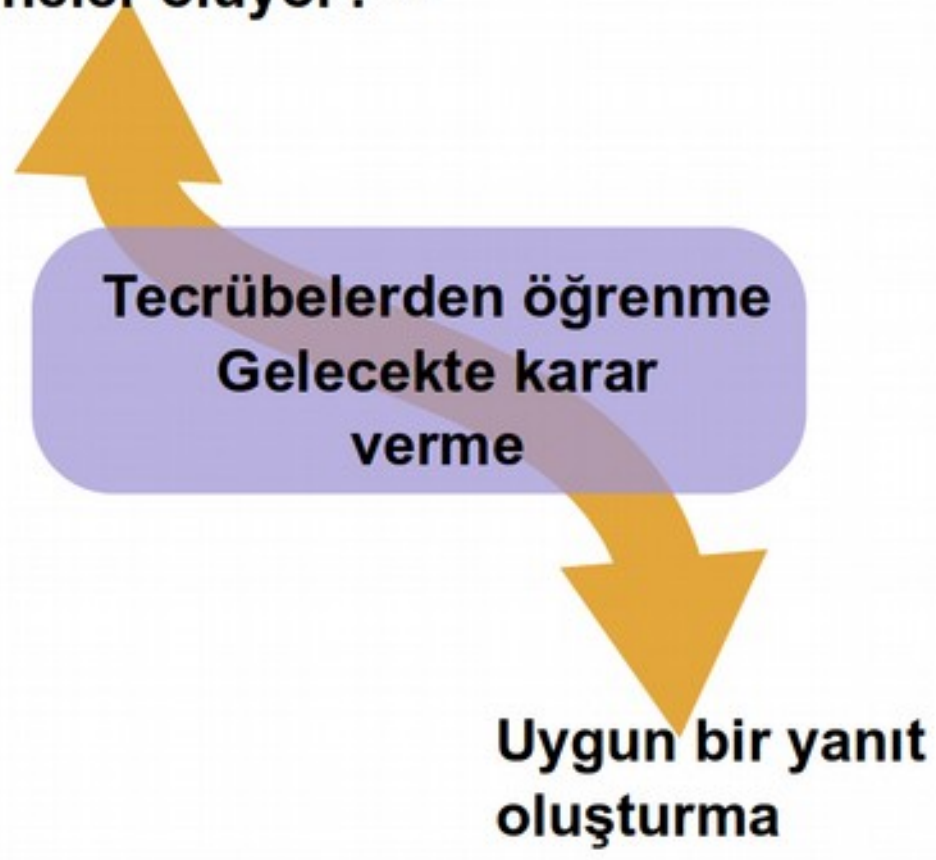


LaSarre B,

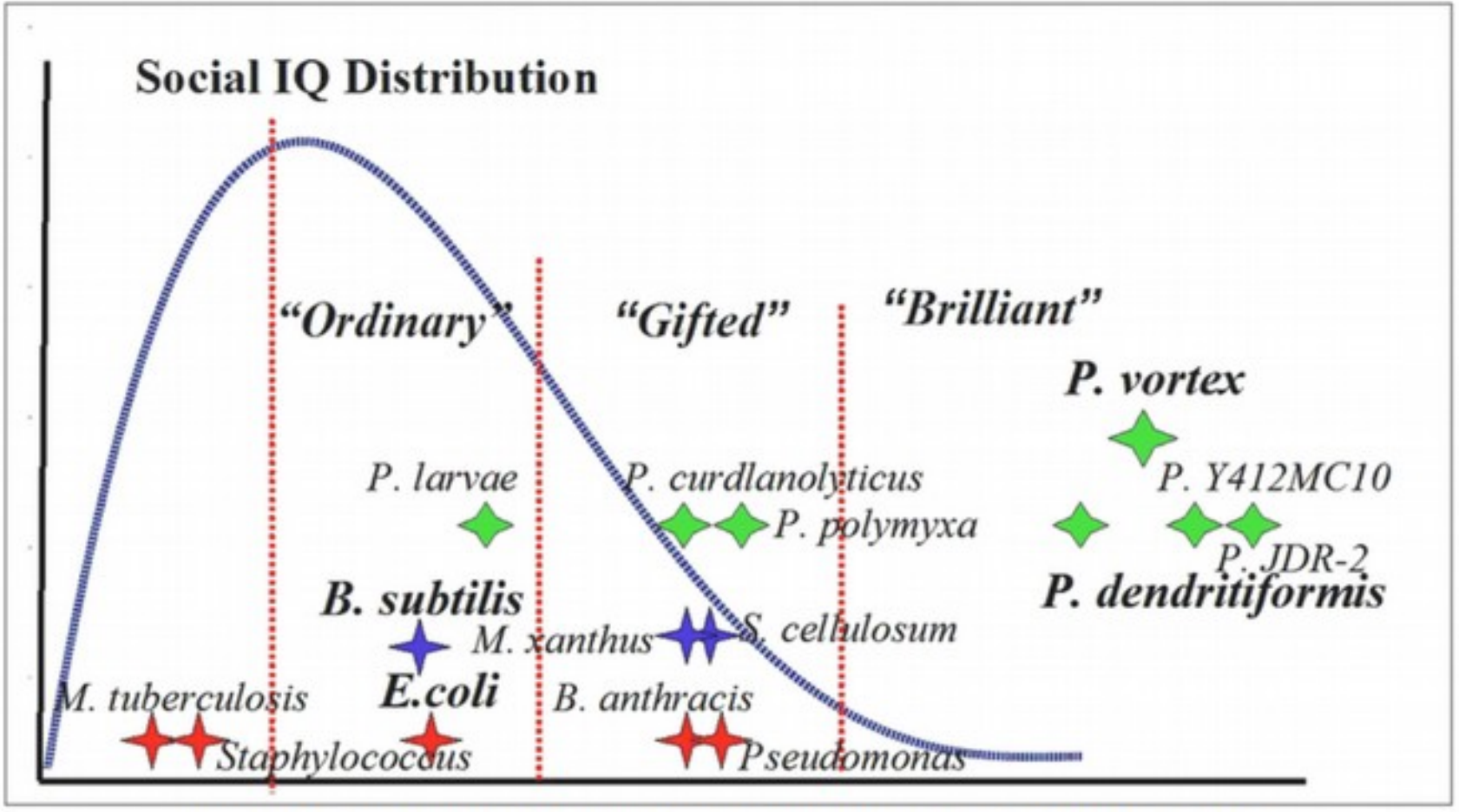
1. Sirota-Madi A, Olender T, Helman Y, Ingham C, Brainis I, Roth D, et al. Genome sequence of the pattern forming Paenibacillus vortex bacterium reveals potential for thriving in complex environments. BMC Genomics. 2010 Dec 17;11(1):710.



Sosyal zeka:
Bireyin çevresini algılama ve anlama kapasitesi
-- etrafta neler oluyor? --



iyi, kötü, çirkin



http://tamar.tau.ac.il/~eshel/html/intelligence_of_Bacteria.html