



# Quantitative Life Science

"Constrained proteome allocation affects coexistence  
in models of competitive microbial communities"

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- Generalize the classical MacArthur's Consumer-Resource (CR) model
- Explain coexistence of more species than resources in the same environment, not from phenomenological laws, but from biological reasons and experiments
- Explain Diauxic Shifts, i.e. the two different growth regimes of a bacterium with two resources

## MacArthur's CR model

$$\begin{aligned}\dot{m}_\sigma &= m_\sigma \left( \underbrace{\sum_{i=1}^{N_R} \nu_i r_i(c_i) \alpha_{\sigma i}}_{\equiv g_\sigma} - q_\sigma \right) & \sigma = 1, \dots, N_S \\ \dot{c}_i &= s_i - \sum_{\sigma=1}^{N_S} \alpha_{\sigma i} r_i(c_i) m_\sigma & i = 1, \dots, N_R\end{aligned}\tag{1}$$

$N_S$  = number of species

$N_R$  = number of resources

$g_\sigma$  = growth rate of species  $\sigma$

$q_\sigma$  = maintenance cost of species  $\sigma$

$s_i$  = supply rate of resource  $i$

$\alpha_{\sigma i}$  = metabolic strategies

$\nu_i$  = efficiency of resource conversion

$r_i(c_i) = \frac{c_i}{K_i + c_i}$  = Monod function

## CEP

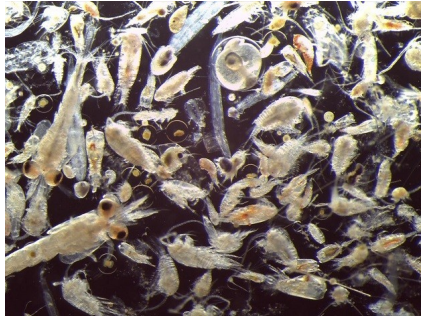
In an environment with  $N_S$  species and  $N_R$  resources, there is coexistence only if  $N_S \leq N_R$ .

- It can be predicted by MacArthur's CR model
- At stationarity ( $\dot{m}_\sigma = 0$ ) we have the system

$$\sum_{i=1}^{N_R} \nu_i r_i(c_i) \alpha_{\sigma i} = q_\sigma$$

which admit solutions only if  $N_S \leq N_R$

- In Nature, many ecosystems violate the CEP
- It has been observed that many plancton species can survive in the ocean, even if the number of available resources is very few!



- MacArthur's CR model predicts CEP. We want to violate it with a **metabolic trade-off**
- Each species has a fixed amount of energy to spend to metabolism  $E = \sum_i w_i \alpha_{\sigma i}$ , where  $w_i$  are the energies spent to uptake resource  $i$
- We suppose the maintenance cost equal to all species  $q_{\sigma} = q$  for all  $\sigma$
- At stationarity ( $\dot{m} = \dot{c} = 0$ ), from the first of equations 1, we can obtain

$$r_i^* = \frac{q}{E} \frac{w_i}{\nu_i} \quad (2)$$

- From the second equations 1, we get the conditions

$$r_i^* = \frac{s_i}{\sum_{\sigma=1}^{N_S} \alpha_{\sigma i} m_{\sigma}^*} \Rightarrow \sum_{\sigma} n_{\sigma}^* \alpha_{\sigma i} = \frac{E}{q} \left( \frac{s_i \nu_i}{w_i} \right) \quad (3)$$

- By defining  $N = \sum_{\sigma} n_{\sigma}$ , we obtain the dynamic equation

$$\dot{N} = \underbrace{\sum_i \overbrace{s_i \nu_i}^{\tilde{s}_i}}_{\tilde{s}} - qN \Rightarrow N^* = \frac{\tilde{s}}{q} \quad (4)$$

# Coexistence conditions in CR model

## Graphical representation



- We rescale the quantities as

$$x_\sigma = \frac{n_\sigma}{N} \quad \hat{\alpha}_{\sigma i} = \alpha_{\sigma i} \frac{w_i}{E} \quad \hat{s}_i = \frac{\tilde{s}_i}{\tilde{s}} \quad (5)$$

- It is clear that they are all normalized as

$$\sum_{\sigma} x_{\sigma} = 1 \quad \sum_i \hat{\alpha}_{\sigma i} = 1 \quad \sum_i \hat{s}_i = 1 \quad (6)$$

- $\vec{\hat{\alpha}}_{\sigma}$  and  $\vec{\hat{s}}$  belong to the  $(N_R - 1)$ -dimensional simplex. Moreover

$$\sum_{\sigma} x_{\sigma}^* \hat{\alpha}_{\sigma i} = \hat{s}_i \quad (7)$$

- We have a geometric interpretation: coexistence is possible only if the rescaled supply rate  $\vec{\hat{s}}$  lies inside the convex hull given by the metabolic strategies  $\vec{\hat{\alpha}}_{\sigma}$

Posfai et al. Metabolic trade-offs promote diversity in a model ecosystem. Phys Rev Lett. 2017; 118:28103

The **proteome**, i.e. the set of proteins synthesized by a species, can be divided in three sectors:

- **P-sector**  $\Rightarrow$  dedicated nutrient uptake and metabolism

$$\varphi^P = \frac{\rho}{k^n r(c)} g \quad (8)$$

- **R-sector**  $\Rightarrow$  dedicated to ribosomal proteins for biomass production and growth

$$\varphi^R = \frac{\rho}{k^t} g + \varphi^0 \quad (9)$$

- **Q-sector**  $\Rightarrow$  dedicated to housekeeping functions

$$\varphi^Q = \text{constant}. \quad (10)$$

Scott et al. *Interdependence of cell growth and gene expression*, Science, 330:1099-1102 (2010)

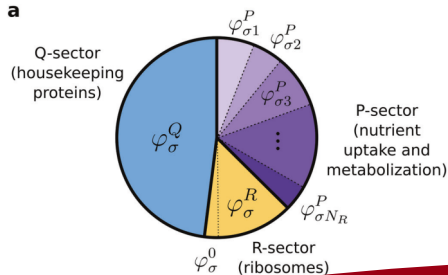


- For multiple species and (substitutable) resources

$$g_{\sigma} = \sum_{i=1}^{N_R} \frac{k_i^n r_i(c_i)}{\rho_{\sigma}} \varphi_{\sigma i}^P \quad \varphi_{\sigma}^R = \frac{\rho_{\sigma}}{k_{\sigma}^t} g_{\sigma} + \varphi_{\sigma}^0 \quad (11)$$

- The normalization condition yields

$$\varphi_{\sigma}^Q + \varphi_{\sigma}^R + \sum_{i=1}^{N_R} \varphi_{\sigma i}^P = 1 \quad \forall \sigma = 1, \dots, N_S \quad (12)$$



By putting all together we get:

$$\sum_{i=1}^{N_R} \varphi_{\sigma i}^P \left[ 1 + \underbrace{\frac{k_i^n}{k_\sigma^t} r_i(c_i(t))}_{\equiv \gamma_{\sigma i}} \right] = \Phi_\sigma \equiv 1 - \varphi_\sigma^Q - \varphi^0$$

$\Downarrow$

$$\varphi_{\sigma i}^P = \varphi_{\sigma i}^P(t) \quad !!$$

For example, for 1 species and 1 resources we have

$$\varphi^P(t) = \frac{\Phi}{1 + \frac{k^n}{k^t} r(c)(t)} , \quad (13)$$

which clearly depends on time.

## CPR model

$$\dot{m}_{\sigma}(t) = m_{\sigma}(t) \left[ \sum_{i=1}^{N_R} \eta_{\sigma i} r_i(c_i(t)) \varphi_{\sigma i}^P(t) - q_{\sigma} \right]$$

$$\dot{c}_i(t) = s_i - \xi_i r_i(c_i(t)) \sum_{\sigma=1}^{N_S} m_{\sigma} \varphi_{\sigma i}^P(t)$$

$$\Phi_{\sigma} = \sum_{i=1}^{N_R} \varphi_{\sigma i}^P \left[ 1 + \gamma_{\sigma i} r_i(c_i(t)) \right]$$

where  $\sigma = 1, \dots, N_S$ ,  $i = 1, \dots, N_R$ ,  $\eta_{\sigma i} = \frac{k_i^n}{\rho_{\sigma}}$  and  $\gamma_{\sigma i} = \frac{k_i^n}{k_{\sigma}^t}$   
 $\xi_i$  is the maximum catalytic rate  $\Rightarrow \alpha_{\sigma i} = \xi_i \varphi_{\sigma i}^P(t)$

**Goal** : determine a condition on  $q_\sigma$  to have coexistence

- Stationarity  $\Rightarrow \dot{m} = \dot{c} = 0$
- From CPR model we have

$$q_\sigma = \sum_{i=1}^{N_R} \eta_{\sigma i} r_i^* \varphi_{\sigma i}^* \quad s_i = \xi_i r_i^* \sum_{\sigma=1}^{N_S} m_\sigma^* \varphi_{\sigma i}^* \quad \Phi_\sigma = \sum_{i=1}^{N_R} \varphi_{\sigma i}^* \left[ 1 + \gamma_{\sigma i} r_i^* \right] \quad (14)$$

- If  $\varphi_{\sigma i}^* \neq 0$  ( $\varphi_{\sigma i} \geq 0$ ) for all  $i$  and  $\sigma$ , then the solution is

$$r_i^* = \left[ k_i^n \left( \frac{\Phi_\sigma}{\rho_\sigma q_\sigma} - \frac{1}{k_\sigma^t} \right) \right]^{-1} \quad (15)$$

- If  $N_S > N_R$  then the RHS of previous equation must be independent on  $\sigma$

$$\frac{\Phi_\sigma}{\rho_\sigma q_\sigma} - \frac{1}{k_\sigma^t} \equiv \theta \quad \forall \sigma = 1, \dots, N_S \quad (16)$$

- From 15 and 16, we get

$$\sum_{i=1}^{N_R} \varphi_{\sigma i}^* = \frac{\Phi_{\sigma}}{1 + \frac{1}{\theta k_{\sigma}^t}} \quad (17)$$

- From 15, we have  $r_i^* = 1/k_i^n \theta$ , which implies  $c_i^* = \frac{K_i}{k_i^n \theta - 1}$ , since  $r_i^* = \frac{c_i^*}{K_i + c_i^*}$
- By definition, we need  $r_i < 1$ , which implies  $\theta > \max_i(1/k_i^n)$
- In the end, we get

$$q_{\sigma} = \frac{\Phi_{\sigma}}{\rho_{\sigma}(\theta + 1/k_{\sigma}^t)} \quad (18)$$

- However, there are solutions also for  $N_S \leq N_R$  and for some null  $\varphi_{\sigma i}^*$ . This happens when  $\vec{\varphi}_{\sigma}^* \cdot \vec{\varphi}_{\rho}^* = 0$  for  $\sigma \neq \rho$

# Coexistence conditions in CPR model

## Graphical representation



- From equations 14, we can define the rescaled quantities

$$\hat{s}_i = \frac{s_i k_i^n / \xi_i}{\sum_{j=1}^{N_R} s_j k_j^n / \xi_j} \quad \hat{\varphi}_{\sigma i}^* = \frac{\varphi_{\sigma i}^*}{\sum_{j=1}^{N_R} \varphi_{\sigma j}} \quad z_\sigma = \frac{m_\sigma^* \rho_\sigma q_\sigma}{\sum_{\lambda=1}^{N_S} m_\lambda^* \rho_\lambda q_\lambda} \quad (19)$$

- From these definitions, it is clear that

$$\sum_i \hat{s}_i = 1 \quad \sum_i \hat{\varphi}_{\sigma i}^* = 1 \quad \sum_\sigma z_\sigma = 1 \quad (20)$$

- Therefore  $\vec{\hat{s}}$  and  $\vec{\hat{\varphi}}_\sigma^*$  belong to the  $(N_R - 1)$  dimensional simplex
- Moreover, from the second of equations 14, we have

$$\hat{s}_i = \sum_{\sigma=1}^{N_S} z_\sigma \hat{\varphi}_{\sigma i}^* \quad (21)$$

- To have coexistence,  $\vec{\hat{s}}$  must belong to the **convex hull** of the vectors  $\vec{\hat{\varphi}}_\sigma^*$
- Coexistence is rooted in values of proteome fractions at stationarity!

How can we adapt the proteome fractions in order to maximize growth rate and satisfy the constraint of total allocation?

- We have a function to be maximized  $Q(\vec{x})$
- The maximization is performed under a strong constraint  $\phi(\vec{x}) = 0$
- The simplest gradient ascent is modified by subtracting the component of  $\vec{\nabla} Q(\vec{x})$  which is parallel to  $\vec{\nabla} \phi(\vec{x})$

$$\dot{\vec{x}} = \vec{\nabla} Q(\vec{x}) - \frac{\vec{\nabla} \phi(\vec{x})}{|\vec{\nabla} \phi(\vec{x})|} \left( \frac{\vec{\nabla} \phi(\vec{x})}{|\vec{\nabla} \phi(\vec{x})|} \cdot \vec{\nabla} Q(\vec{x}) \right)$$

- From **Schwarz inequality**, it is easy to get

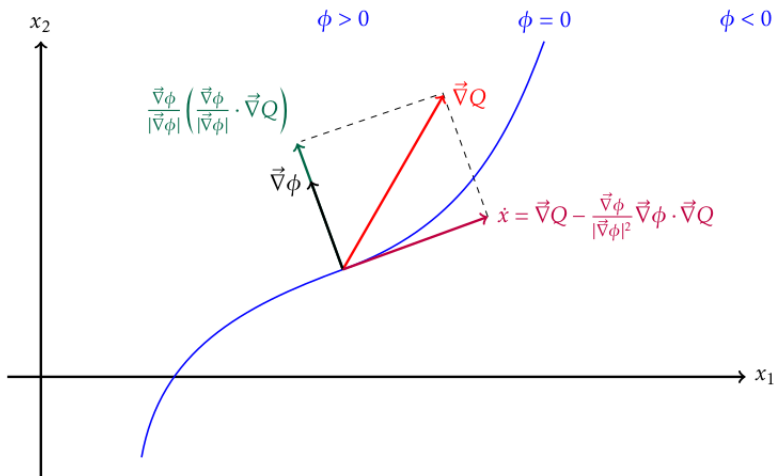
$$\dot{Q}(\vec{x}) = \vec{\nabla} Q(\vec{x}) \cdot \dot{\vec{x}} = |\vec{\nabla} Q(\vec{x})|^2 - \frac{(\vec{\nabla} \phi(\vec{x}) \cdot \vec{\nabla} Q(\vec{x}))^2}{|\vec{\nabla} \phi(\vec{x})|^2} \geq 0$$

- Moreover

$$\dot{\phi}(\vec{x}) = \vec{\nabla} \phi(\vec{x}) \cdot \dot{\vec{x}} = \vec{\nabla} \phi(\vec{x}) \cdot \vec{\nabla} Q(\vec{x}) - \frac{|\vec{\nabla} \phi(\vec{x})|^2}{|\vec{\nabla} \phi(\vec{x})|} \left( \frac{\vec{\nabla} \phi(\vec{x})}{|\vec{\nabla} \phi(\vec{x})|} \cdot \vec{\nabla} Q(\vec{x}) \right) = 0$$

# Strong constrained maximization

## Graphical visualization





- The proteome fractions must depend on time, which means species adapt (not evolve) their metabolic strategies in response to the environment toward different resources depending on their abundances
- The constraint on proteome fractions can be written as

$$F_{\sigma}(\vec{\varphi}_{\sigma}^P(t), \vec{c}(t)) \equiv \sum_{i=1}^{N_R} \varphi_{\sigma i}^P(t) \left[ 1 + \gamma_{\sigma i} r_i(c_i(t)) \right] - \Phi_{\sigma} = 0 \quad \forall \sigma \quad (22)$$

- In particular, by taking the time derivative on both sides, we get

$$\dot{F}_{\sigma}(\vec{\varphi}_{\sigma}^P, \vec{c}) = \dot{\vec{\varphi}}_{\sigma}^P \cdot \vec{\nabla}_{\varphi} F_{\sigma} + \dot{\vec{c}} \cdot \vec{\nabla}_c F_{\sigma} = 0 \quad (23)$$

- The easiest time evolving equation for the adaptive proteome fractions is thus

$$\dot{\vec{\varphi}}_{\sigma}^P = - \frac{\vec{\nabla}_{\varphi} F_{\sigma}}{(\vec{\nabla}_{\varphi} F_{\sigma})^2} \dot{\vec{c}} \cdot \vec{\nabla}_c F_{\sigma} \quad (24)$$

### Goals

- We want to maximize the growth rate for each species  $\sigma$
- The function  $Q(\vec{x})$  becomes

$$g_{\sigma} = \sum_{i=1}^{N_R} \frac{k_i^n}{\rho_{\sigma}} r_i(c_i(t))$$

- We want to constrain the total fraction allocated by each species  $\sigma$  for metabolism and biomass synthesis
- The strong constraint  $\phi(\vec{x})$  becomes the constraint of proteome fractions

$$F_{\sigma}(\vec{\varphi}_{\sigma}^P(t), \vec{c}(t)) \equiv \sum_{i=1}^{N_R} \varphi_{\sigma i}^P(t) \left[ 1 + \gamma_{\sigma i} r_i(c_i(t)) \right] - \Phi_{\sigma} = 0 \quad \forall \sigma \quad (25)$$

- By doing the calculations

$$\dot{\varphi}_{\sigma}^P = \frac{1}{\tau_{\sigma}} \vec{\nabla}_{\varphi} g_{\sigma} - \frac{\vec{\nabla}_{\varphi} F_{\sigma}}{(\vec{\nabla}_{\varphi} F_{\sigma})^2} \left( \frac{1}{\tau_{\sigma}} \vec{\nabla}_{\varphi} g_{\sigma} \cdot \vec{\nabla}_{\varphi} F_{\sigma} + \vec{c} \cdot \vec{\nabla}_c F_{\sigma} \right) \quad (26)$$

- $\tau_{\sigma}$  is the characteristic time scale of metabolic adaption. If it is slow, we expect that species survive only if the rescaled supply rate belongs to the convex hull of proteome fractions
- **Problem:**  $\Rightarrow \varphi_{\sigma i}^P(t)$  could become negative, due to competition between the gradient of growth rate and the constraint
- **Solution:**  $\Rightarrow$  set  $\varphi_{\sigma i}^P$  equal to a non-negative function  $\mathcal{F}(\psi_{\sigma i})$ , where  $\mathcal{F}(x) \geq 0 \forall x$

With  $\mathcal{F}(x) = x^2/4$ , the model eventually reads:

## Constrained maximized CPR

$$\dot{m}_\sigma(t) = m_\sigma(t) \left[ \sum_{i=1}^{N_R} \eta_{\sigma i} r_i(c_i(t)) \varphi_{\sigma i}^P(t) - q_\sigma \right]$$

$$\dot{c}_i(t) = s_i - \xi_i r_i(c_i(t)) \sum_{\sigma=1}^{N_S} m_\sigma \varphi_{\sigma i}^P(t)$$

$$\dot{\varphi}_{\sigma i}^P = \varphi_{\sigma i}^P \left[ \frac{\eta_{\sigma i} r_i(c_i)}{\tau_\sigma} - \frac{v_{\sigma i}}{\sum_k \varphi_{\sigma k}^P v_{\sigma k}^2} \sum_j \varphi_{\sigma j}^P \left( \frac{\eta_{\sigma j} r_j(c_j)}{\tau_\sigma} v_{\sigma j} + \gamma_{\sigma j} \frac{K_j}{(c_j + K_j)^2} \dot{c}_j \right) \right]$$

where  $v_{\sigma i} = 1 + \gamma_{\sigma i} r_i(c_i)$

- In the **CR** model the metabolic strategies are fixed, they do not adapt in time
- Coexistence is possible only if the rescaled supply rate belongs to the convex hull of rescaled metabolic strategies
- In **CPR** model, proteome fractions can adapt in time to allow coexistence, which is possible, under certain conditions, even if the initial rescaled metabolic strategies do not belong to the convex hull of rescaled proteome fractions
- Indeed, coexistence deals with the values of rescaled metabolic strategies at **stationarity**
- The adaptive behaviour of metabolic strategies is rooted in experimental result, it is not ad hoc justification
- The model is able to reproduce, unlike classical CR model, the well known adaptive process of bacteria, leading to a violation of **CEP**. Moreover, it is also able to explain **Diauxic shifts**

We explore three different regimes

- **1** Slow adaptive timescale  $\tau \gg 1$  and low quality nutrients  $\gamma \sim O(0.1)$ . In this conditions, the proteome fitness constraint reads

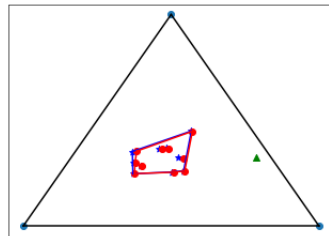
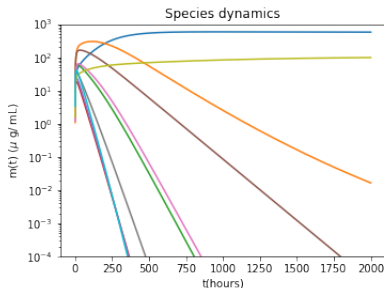
$$\sum_{i=1}^{N_R} \varphi_{\sigma i}^P \simeq \Phi_{\sigma} \quad (27)$$

- We are in the conditions of CR model with metabolic trade-off.
- Since the adaptive timescale is very slow, proteome fractions adapt only to maintain the constraint of total allocation. The adaptive equation reduces to

$$\dot{\varphi}_{\sigma i}^P \approx -\varphi_{\sigma i}^P \frac{v_{\sigma i}}{\sum_k \varphi_{\sigma k}^P v_{\sigma k}^2} \sum_j \varphi_{\sigma j}^P \gamma_{\sigma j} \frac{K_j}{(c_j + K_j)^2} \dot{c}_j \approx 0 \quad (28)$$

- Therefore coexistence is possible only if  $\vec{s}$  belongs to the convex hull of  $\vec{\varphi}_{\sigma}^P$  at the start of dynamics

### Extinctions



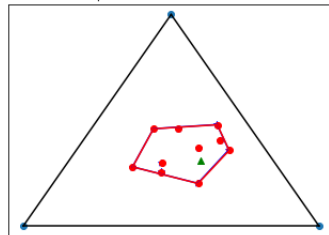
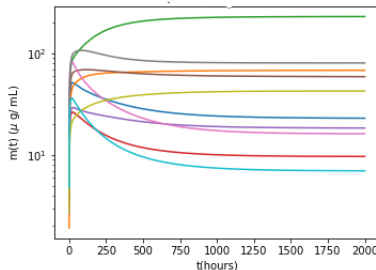
**Figure:** Species dynamics for  $\tau_\sigma \gg 1$  and  $\gamma_{\sigma i} \sim O(0.1)$ . If the rescaled supply rate does not belong to the convex hull of the rescaled proteome fraction, we observe some extinctions.

# Slow adaptive timescale

## Low quality nutrients



### Coexistence



**Figure:** Species dynamics for  $\tau_\sigma \gg 1$  and  $\gamma_{\sigma i} \sim O(0.1)$ . If the rescaled supply rate belongs to the convex hull of the rescaled proteome fraction, we observe coexistence.



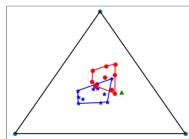
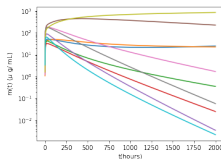
- 2 Slow adaptive timescale  $\tau \gg 1$  and high quality nutrients  $\gamma \sim O(2)$ .

$$\dot{\varphi}_{\sigma i}^P \approx -\varphi_{\sigma i}^P \frac{v_{\sigma i}}{\sum_k \varphi_{\sigma k}^P v_{\sigma k}^2} \sum_j \varphi_{\sigma j}^P \gamma_{\sigma j} \frac{K_j}{(c_j + K_j)^2} \dot{c}_j \not\equiv 0 \quad (29)$$

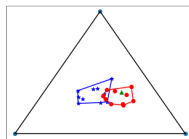
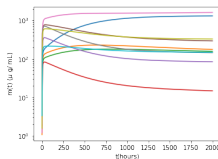
- It is possible for the dynamics of proteome fractions to move  $\hat{s}$  inside the convex hull
- The supply rate  $x\vec{s}$ , for  $x > 1$ , must be sufficiently large
- The rescaled supply rate  $\hat{s}$  must not be too far from the convex hull of proteome fractions

# Slow adaptive timescale

## High quality nutrients



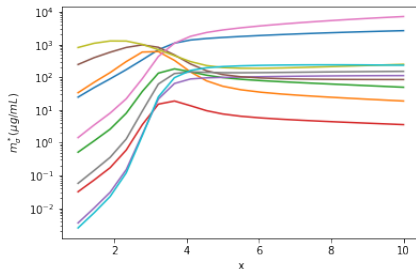
(a)  $x = 1$



(b)  $x = 4$

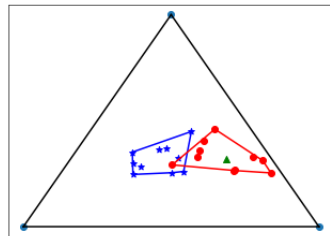
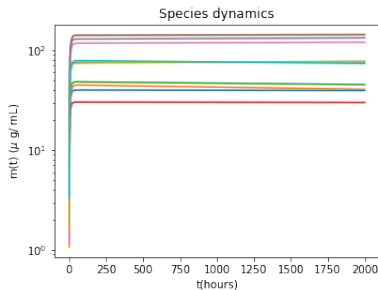
**Figure:** Species dynamics for  $\tau_\sigma \gg 1$  and  $\gamma_{\sigma i} \sim O(2)$ . Coexistence is observed if we multiply the supply rate  $s$  for a factor  $x > 1$  sufficiently large.

# Slow adaptive timescale Transition



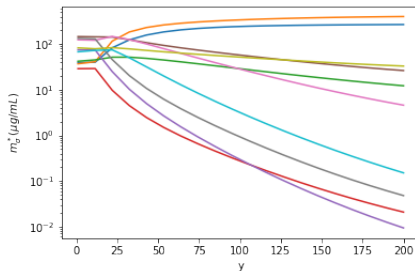
**Figure:** Stationary values of species biomass in function of supply rate rescaling factor  $x$ . We observe coexistence above a critical value  $x \approx 3$ .

- 3 Fast adaptive timescale  $\tau \sim O(1)$  and  $\gamma \sim O(1)$ .
- In this regime, coexistence is always possible, no matter where  $\hat{s}$  is
  - However, as soon as  $\tau$  becomes sufficiently large, fewer species can survive



**Figure:** The adaptive process when  $\gamma \sim O(1)$  and  $\tau \sim O(1)$ .

# Fast adaptive timescale Transition

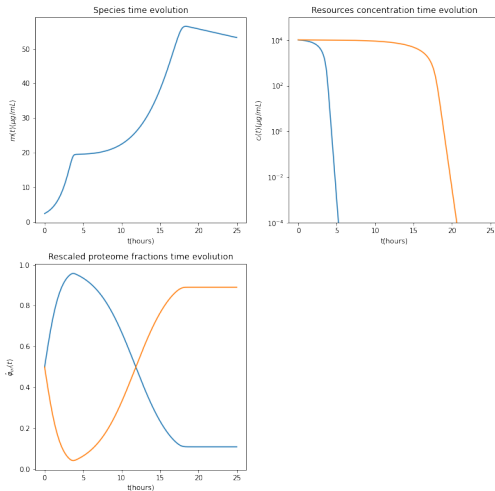


**Figure:** The adaptive by multiplying  $\tau$  for a factor  $y > 1$ . If  $y$  is sufficiently large, we observe extinctions.

- 1 1 species of bacteria (i.e. Escherichia Coli) in an environment with 2 resources, a sugar and a low quality nutrient
- 2 We experimentally observe two regimes of growth
- 3 It cannot be explained by classic **CR** model
- 4 **CPR** predicts the **diauxic shifts**, i.e. the bacteria adapts its metabolic strategies (in this case the proteome fractions) toward the resource with which can grow faster
- 5 As soon as a resource is exhausted, the metabolic strategies vary to consume the other one
- 6 Two exponential growth regimes are predicted

# Diauxic Shifts

## Numerical simulation





- **CPR** model can justify coexistence among species in different regimes
- It is based on biological reasons and does not rely on phenomenological justifications
- It generalize **CR** model with metabolic trade-off in adaptive processes
- It can explain the adaptive behaviour of bacteria competing in an environment with limited resources
- It can explain Diauxic shifts
- It is a minimal modification which can explain coexistence, but different explanations can be also possible

- Supply rates can be dependent on time
- Introduce a spatial scale, in which species can diffuse randomly
- Diffusion according to the concentrations of resources in different areas
- Comprehensive models can be built, in which more elements are present at the same time

Code : [https://github.com/lupoalberto98/QLS\\_project](https://github.com/lupoalberto98/QLS_project)

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Thank you!