

# Metabolic supply chains as Origin for Resistance Development

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## 1. INTRODUCTION

The investigation of very complex dynamical systems like metabolism of an organism requires the comprehension of important subsystems. Here, we investigate metabolic resistances and in particular the link between the geometry of the metabolic network to the impact of environmental changes in the selection of resistant bio types.

## 2. SUPPLY CHAINS UNDER ENVIRONMENTAL INFLUENCES

We introduce a supply chain consisting of different compartments  $A, B, \dots$  whereas each of them can later be interpreted as gen loci in an organism. Each chain posses an inflow in form of  $j_{in}$  into the first compartment and an outflow  $j_{out}$  off the last. Between each compartment is an connection flow  $j$ . All flows are measured against a reference flow  $j$ . Furthermore, we introduce an outer influence  $k(z)$  which connects to  $j$  and is dependent on a toxic xenophobic substance  $z$ . The factor  $z$  inhibits  $k$ , i.e an increase in  $z$  results in a decrease of  $k(z)$ .

In addition, we need more monotony behaviors for the system. We demand that  $j_{in}$  is monotonically decreasing in  $A$  and also  $j_{out}$  monotonically increasing in  $B$ , i.e

$$k \searrow j \searrow j_{in} \searrow A \nearrow \text{ and } k \searrow j \searrow j_{out} \searrow B \searrow .$$

Therefor, we obtain for two compartments the system

$$\begin{aligned} \dot{A} &= j_{in}(A) - j(A, B) \\ \dot{B} &= j(A, B) + j_{out}(B) \end{aligned} \quad (1)$$

with the inflow  $j_{in}(A) = k_{in}(1 - A)$  the outflow  $j_{out}(B) = k_{out}B$  and the connecting flow  $j(A, B) = k(z)(A - B)$ , whereas  $k_{in}$  and  $k_{out}$  are reaction constants.

By scaling  $k_{out}$  and  $k_{in}$  to 1 we get from (1)

$$\begin{aligned} \dot{A} &= (1 - A) - k(z)(A - B) \\ \dot{B} &= k(z)(A - B) + B. \end{aligned}$$

The desired biological effect is that an increase of  $z$  leads to an decrease in  $j$  and finally in an decreased  $j_{out}$ .

The faster time behavior of a metabolic chain grants us a quick adaptation and therefore in the stationary case  $j_{in} = j_{out} = j$ . It is important to remark that this case happens almost immediately in comparison to the heritage and growth of an organism.

By looking at the stationary case and solving it we yield

$$A^* = 1 - \frac{k(z)}{1 + 2k(z)} \Rightarrow j_{out}^* = \frac{1}{2 + k(z)^{-1}}. \quad (2)$$

Hence, an increase of the toxic substance  $z$ , i.e decrease of  $k$ , leads to an decrease of the flow between the compartments.

### 2.1 Different geometries

After getting insight about the basic behavior of a metabolic supply chain we take the next step by analyzing two different forms of connections between the compartments: The 'AND' and 'OR' connections.

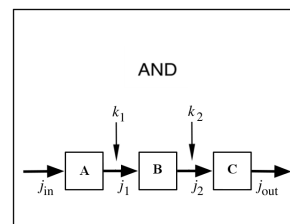


Fig. 1. Illustration of an AND connection

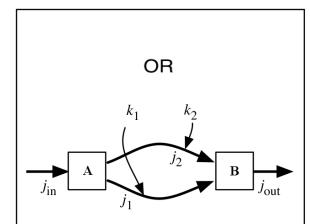


Fig. 2. Illustration of an OR connection

The AND connection is characterized by the continuous sequence of compartments and connecting flows  $j_i$

$$\begin{aligned} \dot{A} &= j_{in}(A) - j_1(A, B) \\ \dot{B} &= j_1(A, B) + j_2(B, C) \\ \dot{C} &= j_2(B, C) - j_{out}(B) \end{aligned}$$

whereas the OR connection has two possible connection between the compartments to simulate the fallback solution of an organism in times of shortage

$$\begin{aligned} \dot{A} &= j_{in}(A) - j_1(A, B) - j_2(A, B) \\ \dot{B} &= j_1(A, B) + j_2(A, B) - j_{out}(B). \end{aligned}$$

Solving again the equations in the stationary case leads similar to (2) to the outflows

$$j_{AND}^* = \frac{1}{2 + k_1^{-1} + k_2^{-1}} \quad j_{OR}^* = \frac{1}{2 + (k_1 + k_2)^{-1}}. \quad (3)$$

As a remark we see that the nature of (3) reminds us of electric circlets, to be more precise: resistances in sequence and parallel connection.

## 3. PROSPERITY OF AN ORGANISM

Next we model the prosperity of a population by the time repented variable  $w(t)$ . Each organism in the population

earns an amount  $j_{out}$  by the metabolism and has a basic level of consumption  $b$ . So we denote  $(j_{out} - b)$  for the reproduction and growth of each organism. Under the assumption of an exponential growth with parameter  $\gamma$  we obtain

$$\dot{w} = \gamma(j_{out} - b)w. \tag{4}$$

The question is now which mortality  $s$  belongs to the growth (4) and this can be solved by comparison to ideal situation  $\dot{w}_{id} = \gamma(j_{out} - b)w_{id} =: f(w_{id})$ . Hence, this leads to

$$\dot{w} = f(w) - sw$$

and translates to

$$\gamma(j_{out} - b)w = \gamma(j_{max} - b)w - sw \tag{5}$$

which describes ideal growth minus the mortality of a population. By solving (5) for  $s$  we obtain

$$s = \gamma(j_{max} - j_{out})$$

which is independent of the wealth  $w$  of a population. Therefore we can interpret a lack of a metabolic product  $j_{out}$  as an increase of mortality  $s$  for the population.

#### 4. CONNECTION OF METABOLIC OUTPUT TO RESISTANCES

In analogy with Langemann (2013) we model a population of biotypes with growth, mortality, and inheritance in a closed domain. The occurrence of the biotypes with index  $i$  in a certain domain is quantified by its population size  $c_i$  depending on the time  $t$ . Each biotype  $i$  is characterized by its growth rate  $w_i > 0$ , a mortality rate  $s > 0$  depending of a xenophobic substance  $z$ . In general, the biotype specific resistances are unknown and so  $s(z)$  were a heuristic approach to the resistance development by Langemann (2013). By using our accumulated results of metabolic chains and their geometry can know give a reason for different resistant behaviors during environmental changes. For better understanding, we will discuss two scenarios for the population dynamic.

Case A is underlined by an AND connection between the gen loci whereas Case B has an OR connection. We denote that  $x_i x_i$  is resistant,  $x_i X_i$  is medium resistant and  $X_i X_i$  is prone to a toxic treatment with  $k_{res} = 1, k_{med} = \frac{1}{4}, k_{pr} = \frac{1}{9}$  and  $i \in \{1, 2\}$ . We use the same parameters for both cases and see at Table 2., im comparison to Table 1. that the combination of a resistant and a susceptible link results in a greatly decreased mortality rate for the OR connection. We interpret this effect as an alternate solution of an organism to deal with the shortage of a product. As last

Table 1. Mortality rates for an AND connection

s	$X_2 X_2$	$X_2 x_2$	$x_2 x_2$
$X_1 X_1$	0.2	0.18	0.17
$X_1 x_1$	0.18	0.15	0.09
$x_1 x_1$	0.17	0.09	0

Table 2. Mortality rates for an OR connection

s	$X_2 X_2$	$X_2 x_2$	$x_2 x_2$
$X_1 X_1$	0.25	0.19	0.05
$X_1 x_1$	0.19	0.15	0.04
$x_1 x_1$	0.05	0.04	0

we compute the behavior of the biotypes with different

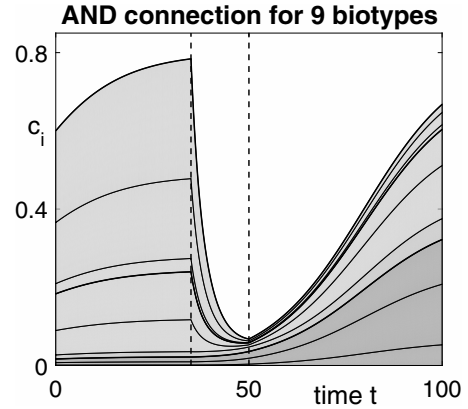


Fig. 3. Only the 3 resistant population gain an advantage after the treatment

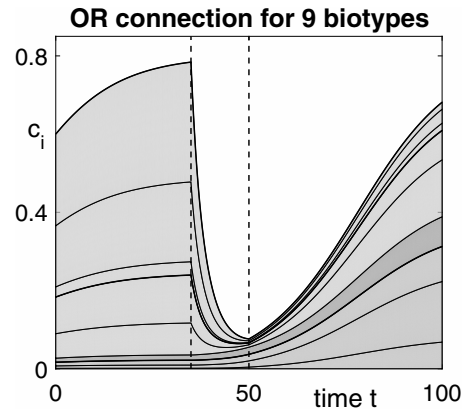


Fig. 4. Better outcome for the medium resistant biotypes after the treatment

mortality rates given by the Tables 1. and 2. As an visual indicator we color the more resistant biotypes in a stronger gray.

As result we remark that biotypes with an OR connection survive better in a changing environment which we can see at Figure 4. ,i.e the middle gray biotypes become larger after the treatment in comparison to a AND biotype with same values.

#### 5. CONCLUSION

Through the usage of metabolic chains we were able to give a mathematical reason for different resistances of certain biotypes under environmental changes. A organism with multiple ways to circumvent a shortage of nutrition can fallback to other sources and therefore handles treatments better than organism with single connections in their metabolism.

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