



Strategic Metabolic Interaction Modeling Reveals Ecological Regimes from Adaptive Resource Exchange

Alex Centeno-Mejía¹, Carolina Marchant Fuentes² & Sara Cuadros-Orellana³

¹Doctorado en Modelamiento Matemático Aplicado, Universidad Católica del Maule, Talca, Chile

²Facultad de Ciencias Básicas, Universidad Católica del Maule, Talca, Chile

³Centro de Biotecnología de los Recursos Naturales, Universidad Católica del Maule, Talca, Chile

Outline

Motivation

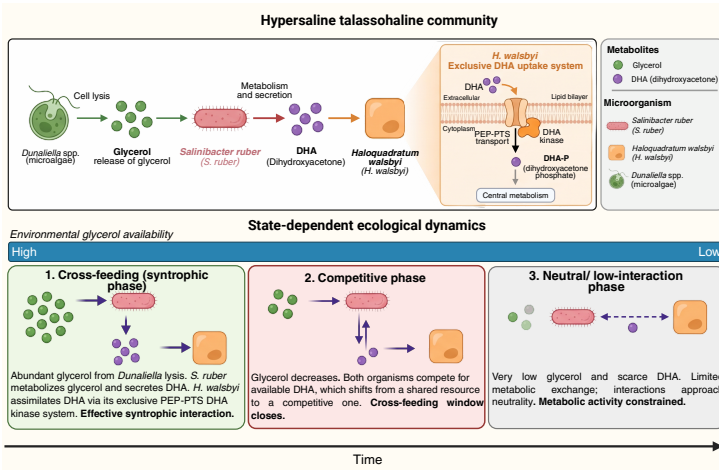
Framework

Synthetic validation

Genome-scale case study

Conclusions

The same pair of microbes can help or hurt each other



- In crystallizer ponds, *S. ruber* turns *Dunaliella* glycerol into DHA, which feeds *H. walsbyi*.
- When glycerol runs out, *S. ruber* can take the DHA back.
- The **sign** of the interaction changes, while the **network** stays the same.

Question

Can facilitation, competition and neutrality be *derived* from metabolism and *tested* statistically?

Hypothesis and objective

Hypothesis

The ecological regime between *S. ruber* and *H. walsbyi* is not a fixed attribute of the pair but an **emergent, state-dependent property** of intracellular metabolism coupled to population and environmental dynamics.

Sub-hypotheses

- H1 The net exchange changes sign when the resource state crosses a threshold, without any parameter change.
- H2 Phenotypic heterogeneity rescales the interaction but never inverts it.
- H3 Regimes, and hidden interaction channels, are identifiable from data under conditions that can be stated in advance.

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Objective

Develop the **Strategic Metabolic Interaction Model (SMIM)**: a framework in which interaction regimes emerge from genome-scale metabolism, phenotypic heterogeneity and partially observed exchange, and are tested statistically.

SMIM framework

Each population optimizes its own metabolism

$$\Phi_i = \max_{\mathbf{v}_i \in \mathcal{F}_i(\mathbf{E})} \text{biomass}(\mathbf{v}_i) \quad (\text{genome-scale LP})$$

Growth averages over traits and beliefs

$$\bar{\mu}_i = \iint \Phi_i \underbrace{\pi_i(\boldsymbol{\theta})}_{\text{phenotypes}} \underbrace{b_i(\mathbf{M}_i)}_{\text{beliefs}} d\boldsymbol{\theta} d\mathbf{M}_i$$

Populations and shared metabolites

$$\dot{X}_i = X_i(\bar{\mu}_i - \delta_i), \quad \dot{E}_k = \text{release} - \text{uptake} - \delta_k E_k$$

Interaction operator

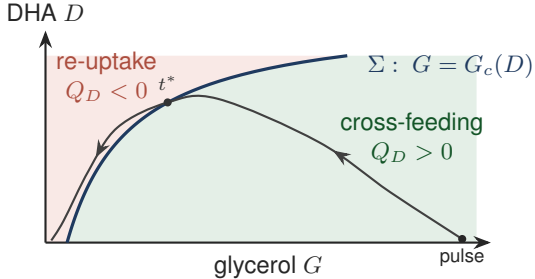
$$\mathcal{J}_{ij} = \frac{\partial \bar{\mu}_i}{\partial u_j}$$

$\mathcal{J}_{ij} > 0$ facilitation $\mathcal{J}_{ij} < 0$ competition

$\mathcal{J}_{ij} = 0$ neutrality

- Traits π_i follow a replicator equation.
- Beliefs b_i over unobserved channels follow a transport–replicator (Bayesian) equation.
- Strategic layer: non-cooperative differential game.

Proposition 1: the switch is induced by the state



Net DHA flux of *S. ruber*

$$Q_D = X_S \left[\underbrace{\alpha_{SS} v_{S,G}(G)}_{\text{release}} - \underbrace{\sigma_{S,D}(D)}_{\text{recapture}} \right]$$

- (i) $Q_D > 0 \iff G > G_c(D)$: the regime is decided by the **position of the state**, not by a parameter.
- (ii) The facilitation channel $\mathcal{J}_{H,S} \geq 0$ **never reverses**; only the net balance does.
- (iii) $Q_D = \dot{D} + \text{uptake}_H + \text{loss}$: competition can only consume DHA **accumulated earlier**, so it is **transient and self-limiting**.

In the genome-scale model Σ becomes the vertical line $G = G_c^{\text{GSMM}} = 0.75 \text{ mM}$.

Heterogeneity and inference

Proposition 2 (robustness)

For any trait distribution with finite variance,

$$\text{sign } \mathcal{J}_{H,S} = \text{sign } \mathcal{J}_{H,S}^{(0)}.$$

Every phenotype benefits from more DHA, so averaging can rescale the benefit but never turn it into a cost.

Inference on autocorrelated trajectories

Neutrality test

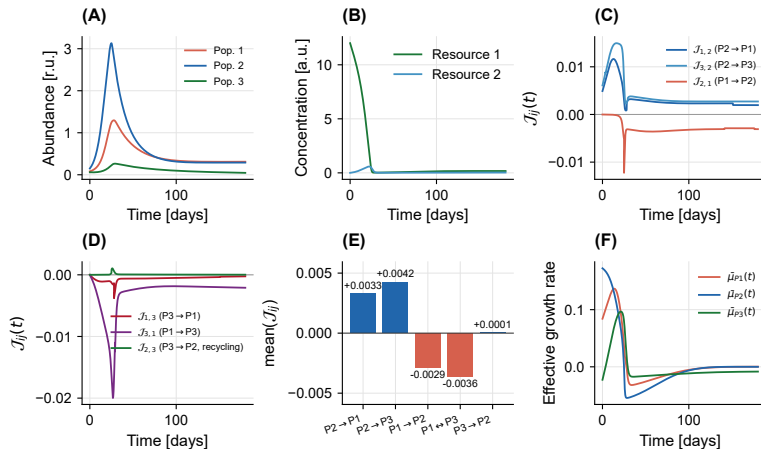
$$Z_{ij} = \frac{\sqrt{T} \bar{\mathcal{J}}_{ij}}{\hat{\sigma}_{ij}^{\text{HAC}}} \xrightarrow{d} \mathcal{N}(0, 1)$$

Bilateral test

$$\mathfrak{W}_{ij} \xrightarrow{d} \chi_2^2$$

Newey–West long-run variance; tests applied **within each regime window**.

Synthetic community: opposite signs at the same time

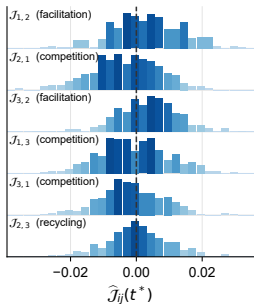


Pair	$\bar{J}_{ij}$	Z_{ij}
$P_2 \rightarrow P_1$	+0.0033	+25.8
$P_2 \rightarrow P_3$	+0.0042	+23.3
$P_1 \rightarrow P_2$	-0.0029	-47.5
$P_3 \rightarrow P_1$	-0.0006	-32.0
$P_1 \rightarrow P_3$	-0.0031	-18.6
$P_3 \rightarrow P_2$	+0.00005	+8.7

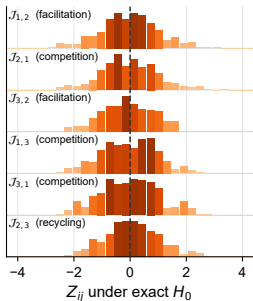
All six directions recovered with the correct sign ($p < 0.001$), **without telling the estimator the topology.**

The tests are calibrated

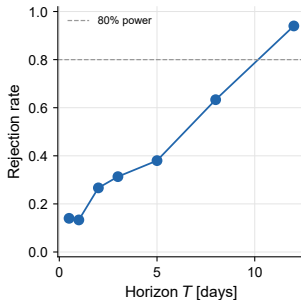
(A)



(B)



(C)



1.7–6.7%

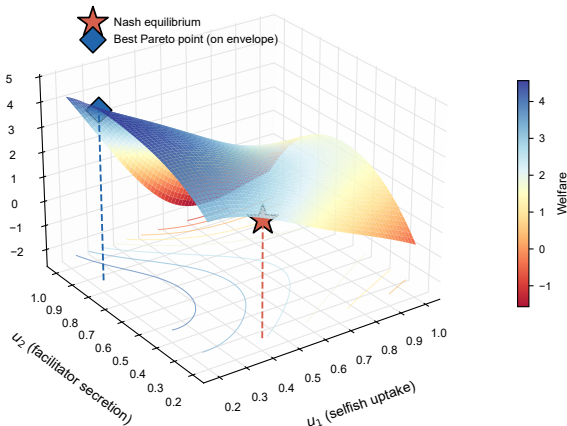
empirical size
(nominal 5%)

94%

power at $T = 12$ d

300 replicates per channel under exact nulls; bias $< 15\%$ of the Monte Carlo s.d.

When secretion is costly, cooperation is a public good



- Nash equilibrium: the facilitator secretes the **minimum** ($u_2 = 0.20$).
- A coordinated (Pareto) profile would raise total welfare by

+91%

Nash $\rightarrow$ Pareto (synthetic triad)

Does the real consortium face the same dilemma?

Two genome-scale models, solved at every time step

Models

- *S. ruber*: iSR780, curated
2461 reactions, 1622 metabolites
- *H. walsbyi*: iHQW-TK
1873 reactions, 1313 metabolites

Curation of *S. ruber*

- Glycerol could not enter the cell: added *GlpF*.
- DHA had no transport: added DHA export/uptake.
- Quality control (MEMOTE):
stoichiometrically consistent, **no energy-generating cycles**.

No secretion rule is imposed

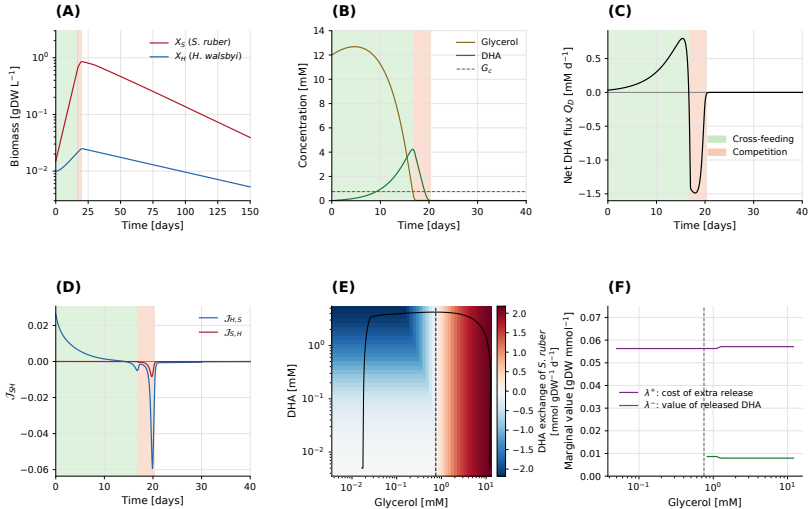
A single capacity limits C_3 assimilation in *S. ruber*:

$$v_{\text{GLYK}} + v_{\text{ALCD19}} + v_{\text{DHAPT}} \leq C_{\text{assim}}$$

Excess glycerol is oxidized to DHA **only if it pays**. The switching line follows directly:

$$G_c^{\text{GSMM}} = \frac{K_{S,G} C_{\text{assim}}}{q_{S,G}^{\text{max}} - C_{\text{assim}}} = 0.75 \text{ mM}$$

The regime switch emerges from the linear programs



Facilitation → competition → neutrality

16.7 d

cross-feeding
(11% of the run)

3.7 d

competition: recaptures 3.9 of
the 4.2 mM pooled earlier

17%

of released DHA
reaches *H. walsbyi*

Tests within each regime window

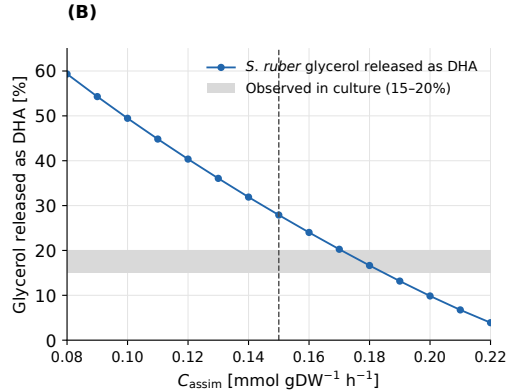
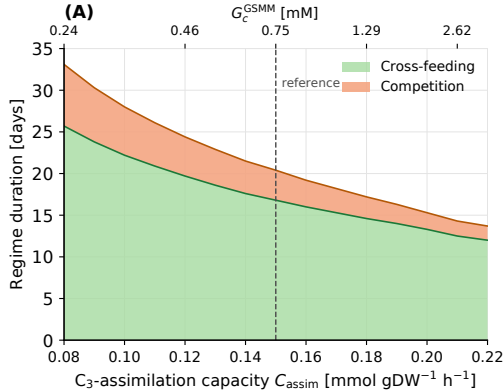
Window	Z_{HS}	Z_{SH}	Reading
Cross-feeding	+4.55	-3.08	asymmetric syntrophy
Competition	-2.49	-2.92	reciprocal competition
Neutral	n.s.	n.s.	substrates exhausted

- Over the whole run the two phases **cancel** ($Z_{HS} = +0.45$): partition first, then test.
- The LP prices the release: retaining DHA would *cost* *S. ruber* growth ($\lambda^- > 0$).

Reading

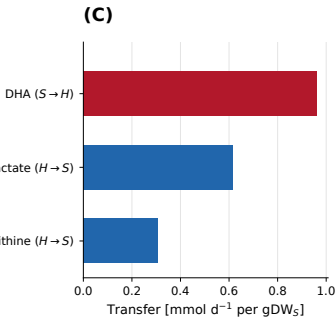
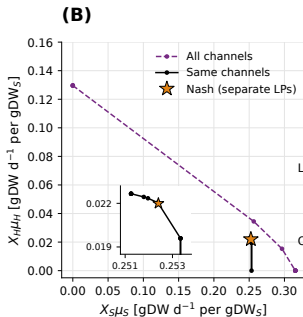
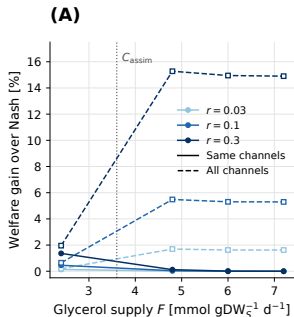
DHA release is a **by-product of overflow**, not costly cooperation; competition is **borrowed from the past**.

The threshold is set by the producer



- The timing of the switch depends on the *S. ruber* glycerol side (C_{assim} , $q_{S,G}^{\text{max}}$).
- *H. walsbyi* kinetics change *how much* DHA it gets, not *when*.
- The 15–20% DHA release measured in culture is matched at $C_{\text{assim}} \approx 0.17\text{--}0.18 \text{ mmol gDW}^{-1} \text{ h}^{-1}$.

Nash vs. Pareto in the real consortium



Same exchange channels (glycerol, DHA)

Nash $\approx$ Pareto: gain $< 0.12\%$. Overflow already gives what a planner would choose.

All 337 shared metabolites

Planner gains up to 15% only by stopping one partner's growth (lactate, ornithine return): an artifact of a joint objective.

Proposition 3: what growth data can and cannot reveal

Hidden channel $H \rightarrow S$: an effect no LP can express (e.g. toxicity).

(i) Structural

If the donor cannot secrete the candidate metabolite, that hypothesis is **indistinguishable from neutrality**, whatever the data. *H. walsbyi* cannot make glutathione $\Rightarrow$ only methylglyoxal remains.

(ii) Statistical

Learning is set by the **Fisher information** $\eta \int M^2 / \sigma^2 dt$: hypotheses must differ by $> 0.67 \sigma$ per observation.

Methylglyoxal along the GSMM run

$$\leq 3 \mu\text{M}$$

signal if *H. walsbyi* keeps 99% of its growth (inhibition starts near 0.3 mM)

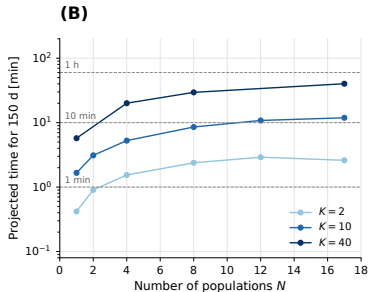
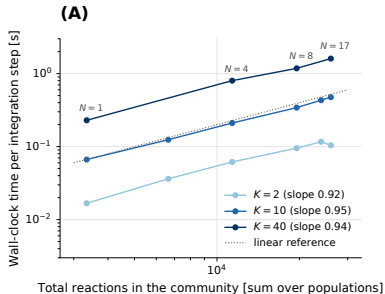
$$\leq 0.40$$

posterior on inhibition, even with 2% growth-measurement noise

Experimental reading

Growth data cannot resolve this channel: **measure methylglyoxal directly** in co-culture.

It scales to communities



17 halophilic taxa, 23 334 reactions, one LP per population per step.

$\approx$ **linear**

cost vs. network size
(slope 0.92–0.95)

2.6–40 min

for 150 d, single core

Take-home messages

1. **Interaction sign is a property of the state, not of the species.**

It switches when the state crosses an explicit curve; competition draws on DHA pooled earlier and fades by itself; heterogeneity cannot invert the sign.

2. **Regimes are testable, and hidden channels have explicit limits.**

HAC tests work within regime windows; the reconstructions tell in advance which hidden channels growth data can resolve.

3. **The same framework separates two kinds of cooperation.**

Costly secretion is an under-provided public good (+91%); overflow release in *S. ruber*–*H. walsbyi* is already efficient.

SMIM turns “who helps whom” from a model *input* into a model *prediction*.

Limitations and next steps

Calibration

- A single glycerol pulse favors *S. ruber*, whereas *H. walsbyi* dominates real crystallizers.
- Next: sustained oligotrophic supply and field-based loss rates.

Hidden $H \rightarrow S$ channel

- Glutathione lacks donor support; methylglyoxal is too weak to detect from growth.
- Add the missing transports in *H. walsbyi* and measure the metabolites.

Experiments

- Co-culture metabolomics: DHA, glutathione, methylglyoxal, lactate, ornithine.
- Estimate $\mathcal{J}_{ij}$ from longitudinal time series.

Methods

- Heterogeneity in both populations.
- Strategies that also optimize information (dual control); spatial structure.

Thank you

Questions and comments are welcome

alex.centeno@alumnos.ucm.cl • github.com/AICenme1

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Backup: why does *S. ruber* dominate in the single-pulse run?

Diagnosis (resource-ratio R^* argument)

- With low-affinity glycerol uptake, *H. walsbyi* cannot persist on glycerol ($\mu_{\max} < \delta_H$).
- DHA overflow supplies only $\approx 5\%$ of the carbon.
- A single large pulse favors the fast opportunist (*S. ruber*).

Exploratory crystallizer runs (4 years)

- High-affinity glycerol uptake (*gleaner*) and frequent small pulses: *H. walsbyi* reaches 90% of biomass.
- Trade-off: the better *H. walsbyi* competes for glycerol, the less it depends on DHA.
- Calibration against field abundances is in progress.

Backup: phenotypic heterogeneity and the sign of $\mathcal{J}_{H,S}$

99.93%

of time steps: sign of $\mathcal{J}_{H,S}$ unchanged
by heterogeneity in *H. walsbyi*

6.2%

largest magnitude correction

- The single disagreement is at the zero crossing ($t = 14.4$ d), where both values are $< 10^{-4} \max |\mathcal{J}_{H,S}|$.
- Heterogeneity moves the crossing by one step (0.1 d); it does not invert the sign, as Proposition 2 predicts.

Backup: why the competition window is short

Mass balance of the DHA pool

$$\dot{D} = Q_D - u_H X_H - \delta_D D \implies Q_D < 0 \Rightarrow \dot{D} < 0$$

Over a competition window (a, b) :

$$\int_a^b |Q_D| dt \leq D(a) - D(b) \leq D(a)$$

(Supplementary Theorem S7.6)

4.2 mM

DHA pool when competition starts
($t = 16.7$ d)

3.9 mM

recaptured by *S. ruber* in 3.7 d

A quasi-stationary pool would never produce
a competition phase.