Metabolic Cross-feeding in the Gut Microbiota

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18-Dec-2019

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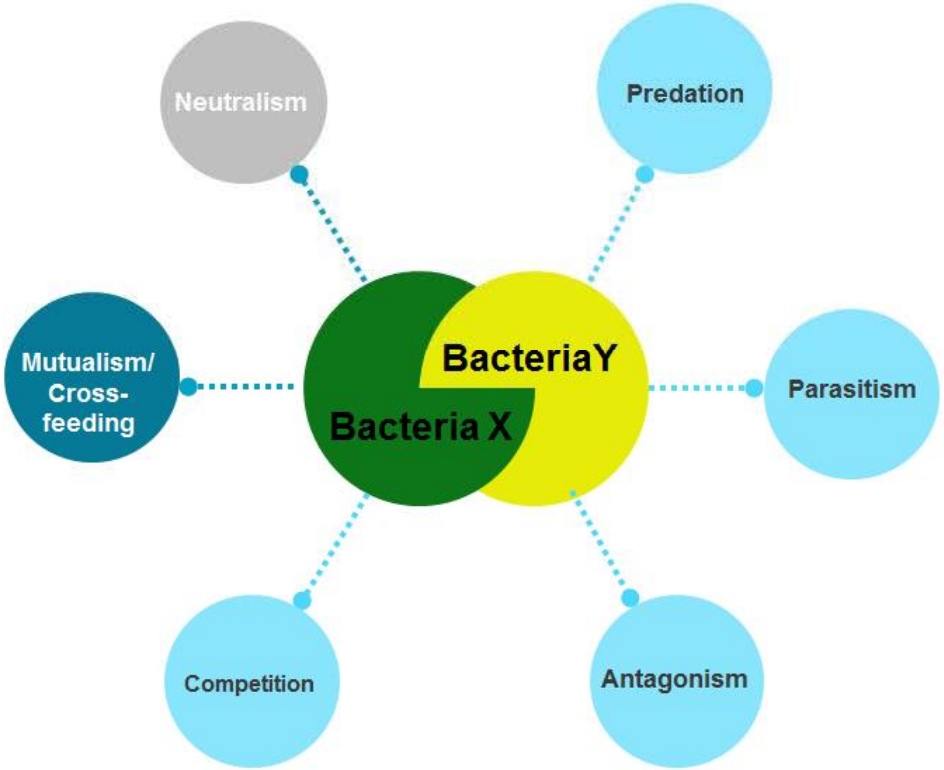
1. What is cross-feeding in bacteria?
2. Classification of cross-feeding.
3. Molecular mechanism: three examples.
4. Evolution and maintenance of cross-feeding.
5. Significances of cross-feeding in bacteria.

People interaction

On earth…

- **World population:** 7.7 billion in 2019
- **Six degrees of separation theory:** state that all people are six, or fewer, social connections away from each other.
- **People interaction:** closely connected with others

Bacterial interactions



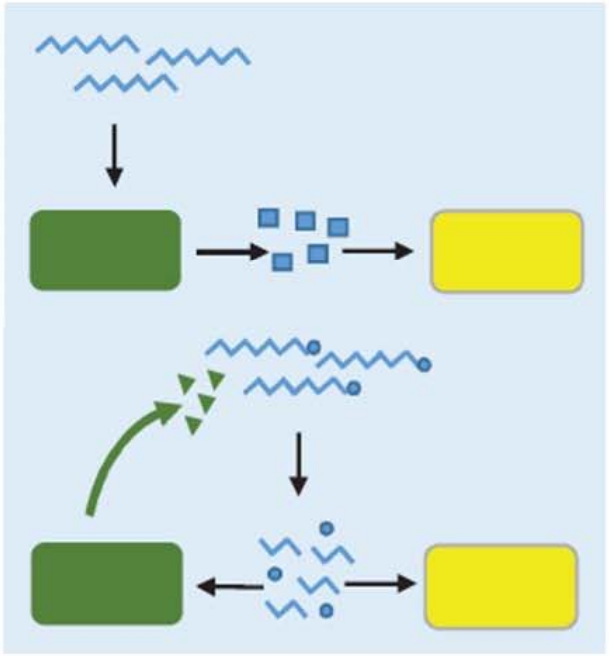
In microbial world…

- Six bacterial interactions have been described.
- Competitive interactions are the dominant interaction.
- Mutualistic interaction/cross-feeding…

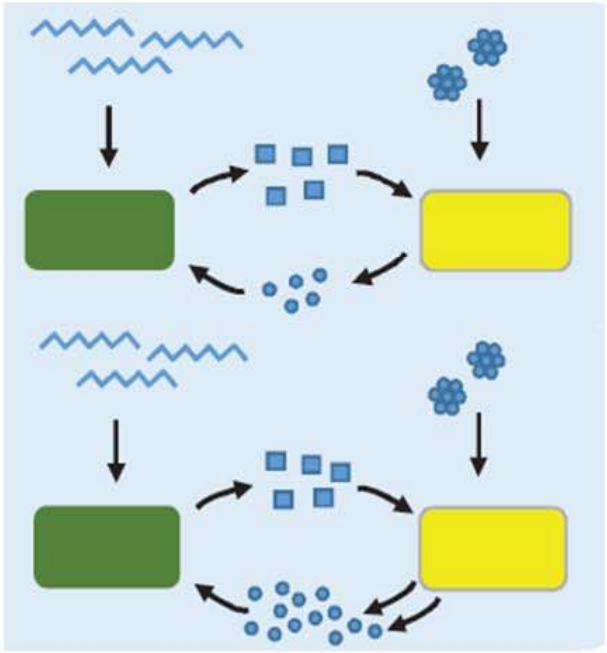
Karsten Zengler and Livia S. Zaramela, 2018, Nature review

Classification of cross-feeding interactions

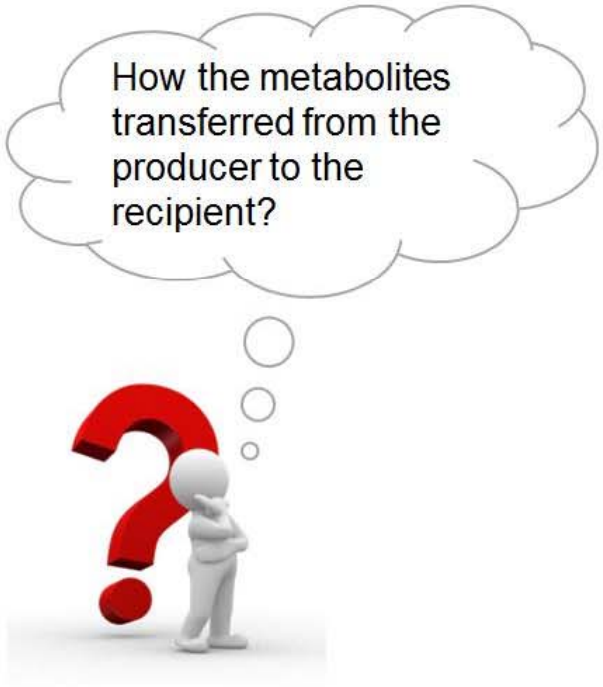
◆ **Mutualism/cross-feeding:** bacterial interaction that involved an exchange of molecules and benefit from one another.



Unidirectional

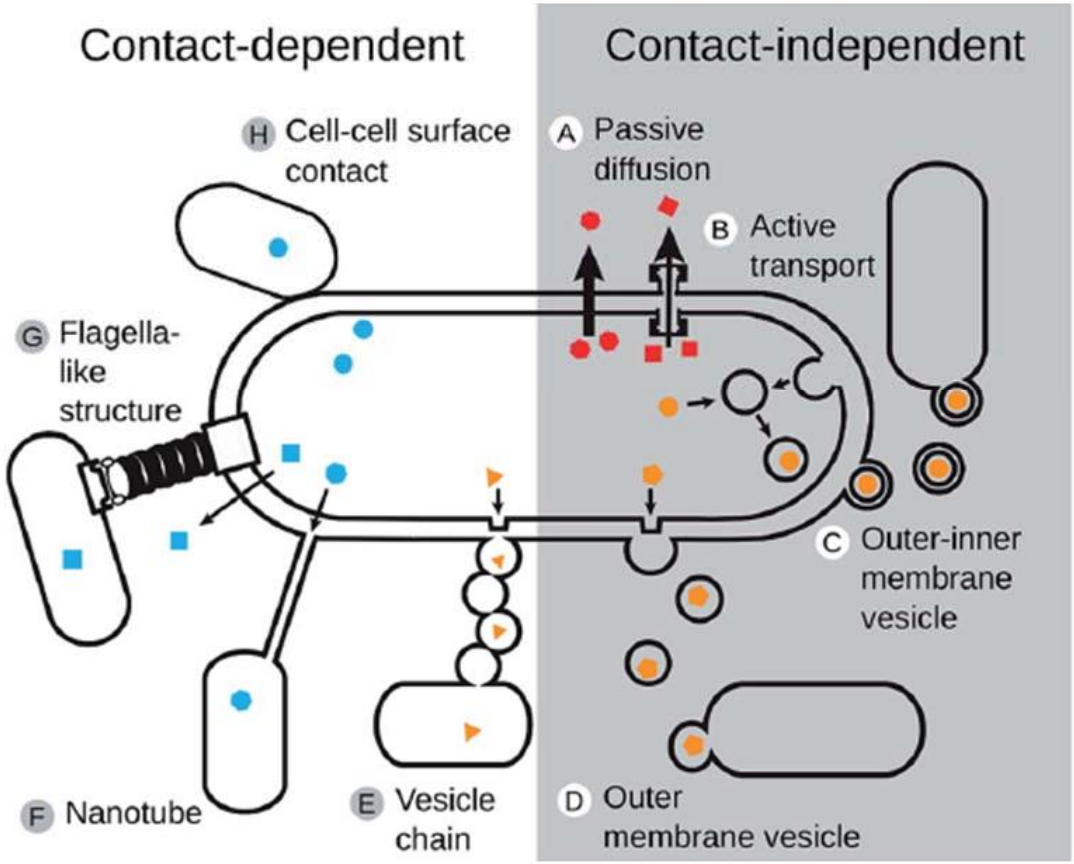


Bidirectional



Warren C. McNabb et al. 2019.,Frontiers in Ecology and Evolution.

Mechanisms of metabolite transfer

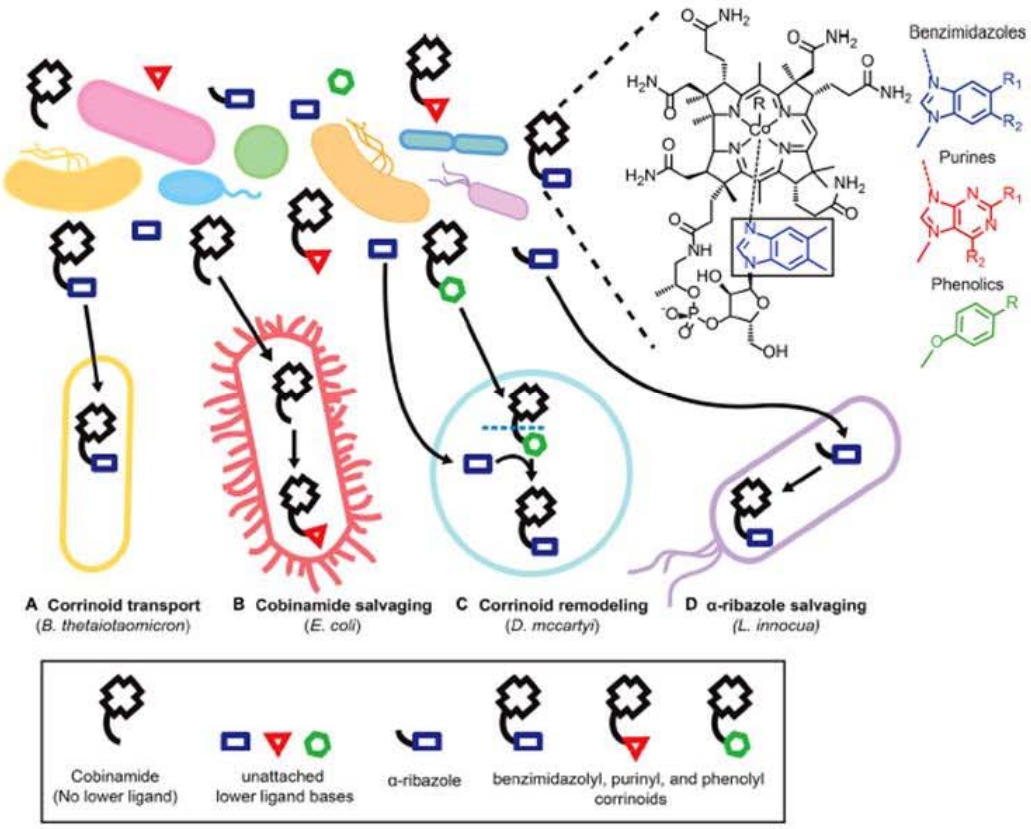


A. **Small molecules, no ATP :** hydrogen, formate, potassium, methanol as well as metabolites like vitamins, acetate, amino acids, and intermediates of the TCA cycle.

B. **ATP**: some amino acids, siderophores, enzymes, polymers, and **corrinoid.**

Christian Kost et al., 2018. Natural Products report

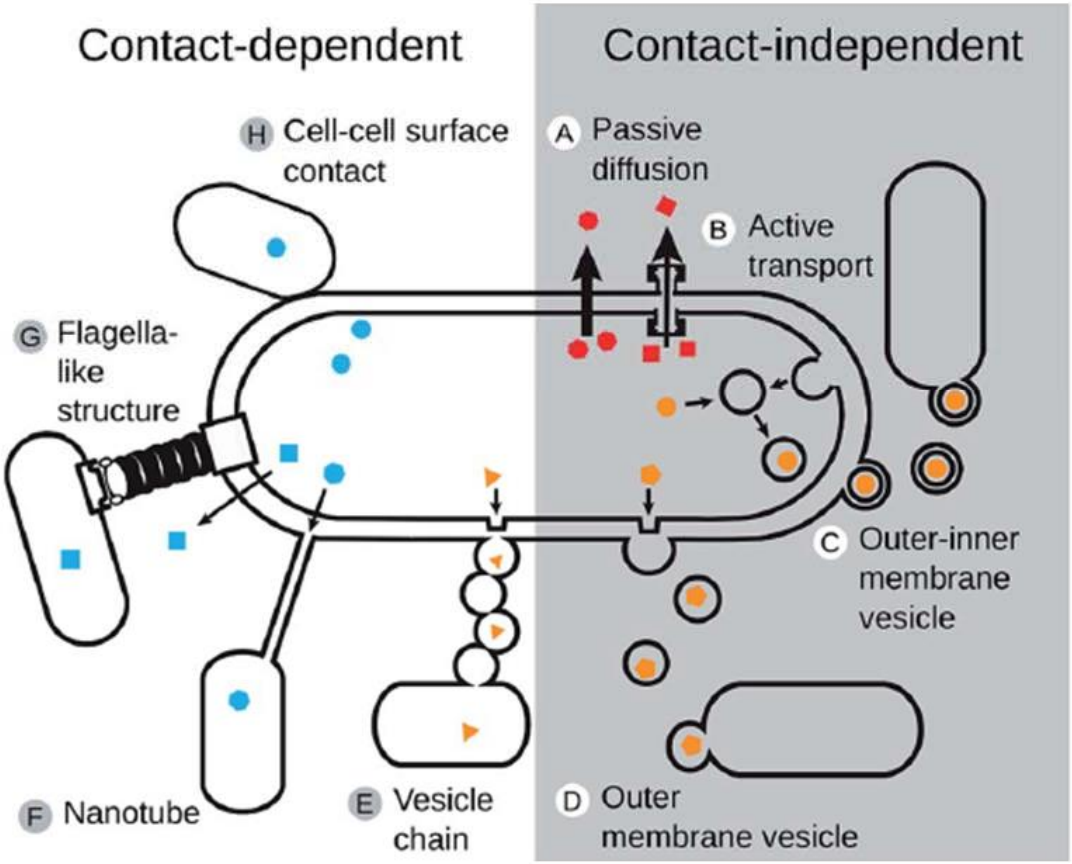
Example: cross-feeding in corrinoid



- **Corrinoids,** such as vitamin B12, play an important role in DNA synthesis, fatty acid and amino acid metabolism.
- At least half of the gut microbiota lack the ability to produce corrinoids *de novo*. (?)
- *B. thetaiotaomicron* contains multiple transporter for the uptake of externally available vitamin B12.
- Cobinamide **salvaging** in *Escherichia coli*, corrinoides **remodeling** in *Dehalococcoides mccartyi*.

EricaC.Seth and Michiko E.Taga 2014. Frontier in Microbiology

Mechanisms of metabolite transfer



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C-E. via **OMVs**

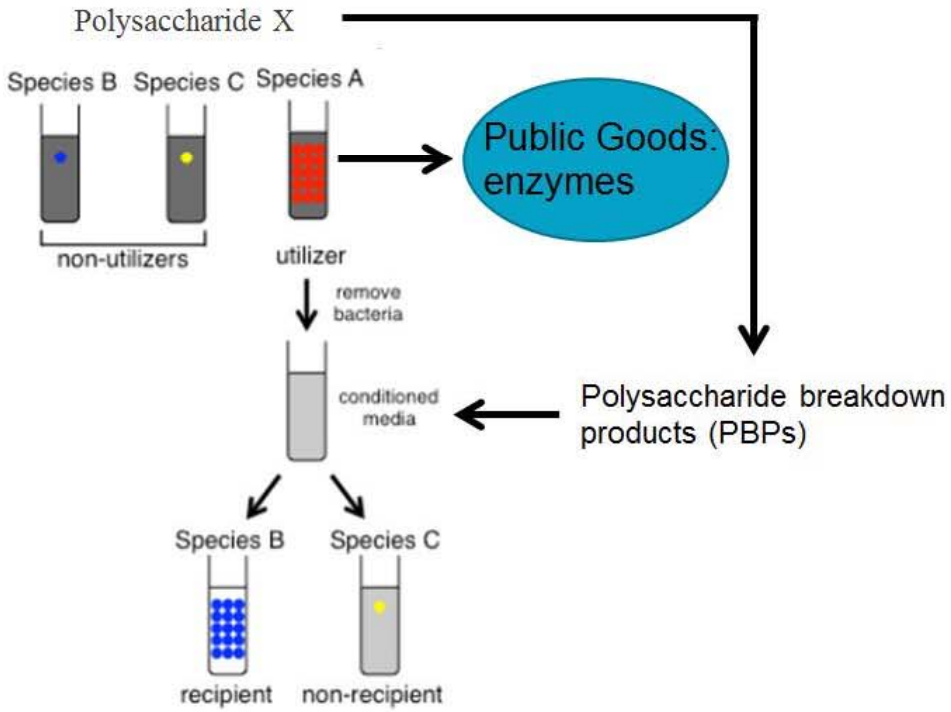
- Shuttles for transferring virulence factors.
  - Transfer public goods in polysaccharides metabolism.

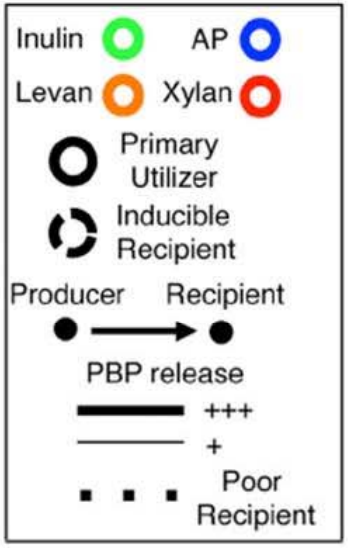
Christian Kost et al., 2018. Natural Products report

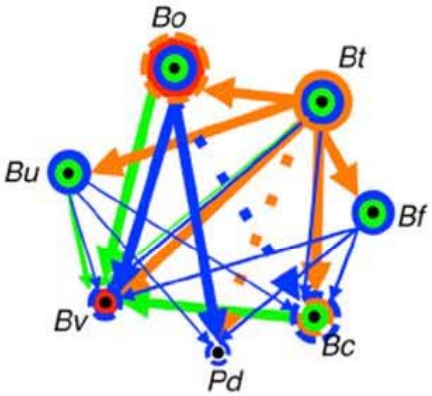
Example: cross-feeding in polysaccharide utilization

Current Biology
Volume 24, Issue 1, 6 January 2014, Pages 40-49

An Ecological Network of Polysaccharide Utilization among Human Intestinal Symbionts



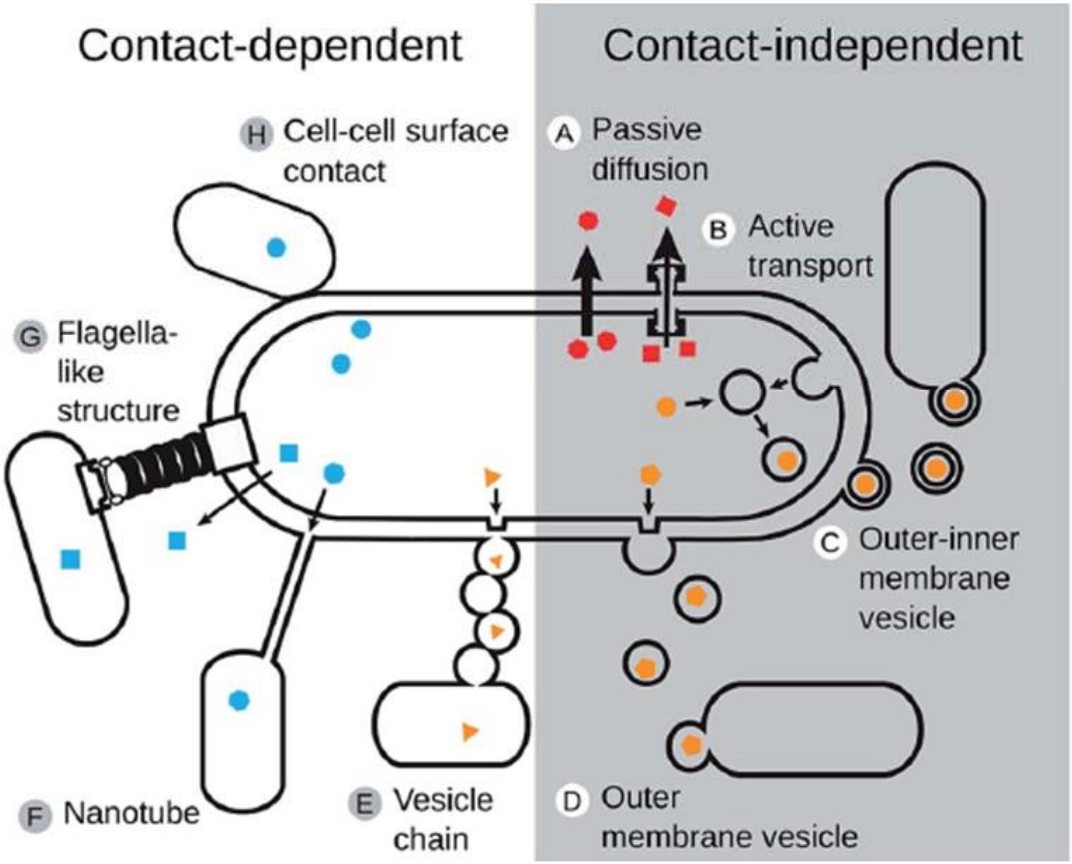




B. caccae (*Bc*)
B. fragilis (*Bf*)
B. ovatus (*Bo*)
B. thetaiotamicron (*Bt*)
B. uniformis (*Bu*)
B. vulgatus (*Bv*)
P. distasonis (*Pd*)

OMVs format: polysaccharide-degrading enzymes secreted by the utilizers in the format of OMVs.

Mechanisms of metabolite transfer



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F. via **nanotube**

Christian Kost et al., 2018. Natural Products report

Example: cross-feeding via nanotubes

nature COMMUNICATIONS

Received 14 Aug 2014 | Accepted 8 Jan 2015 | Published 23 Feb 2015

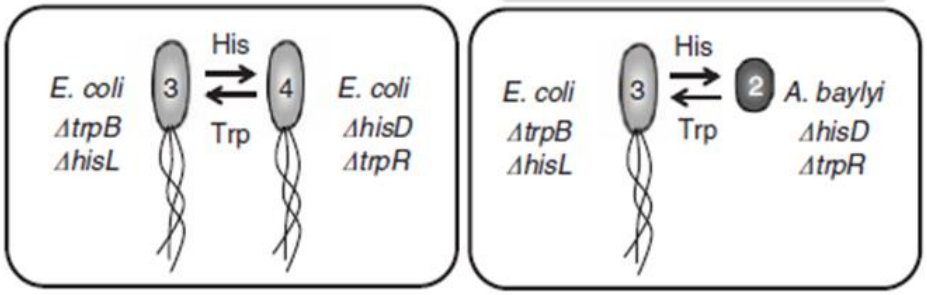
DOI: 10.1038/ncomms7238

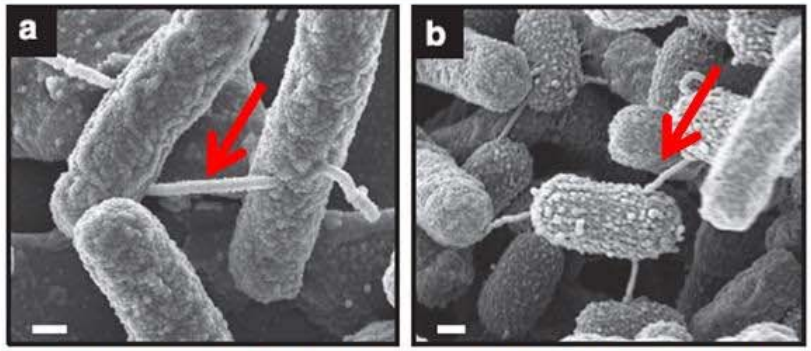
Metabolic cross-feeding via intercellular nanotubes among bacteria

Samay Pande[1,*], Shraddha Shitut[1,*], Lisa Freund[1,*], Martin Westermann[2], Felix Bertels[1], Claudia Colesie[3], Ilka B. Bischofs[4,5] & Christian Kost[1]

Auxotrophs: *ΔtrpB* and *Δ hisD*

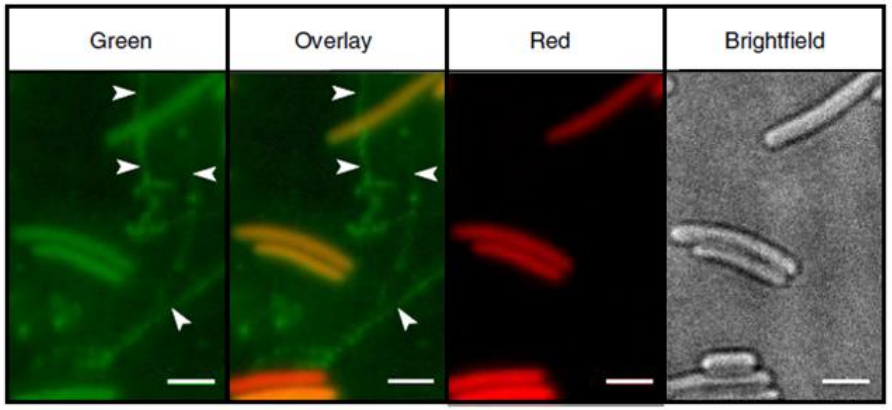
Overproducers: *Δ hisL* and *Δ trpR*





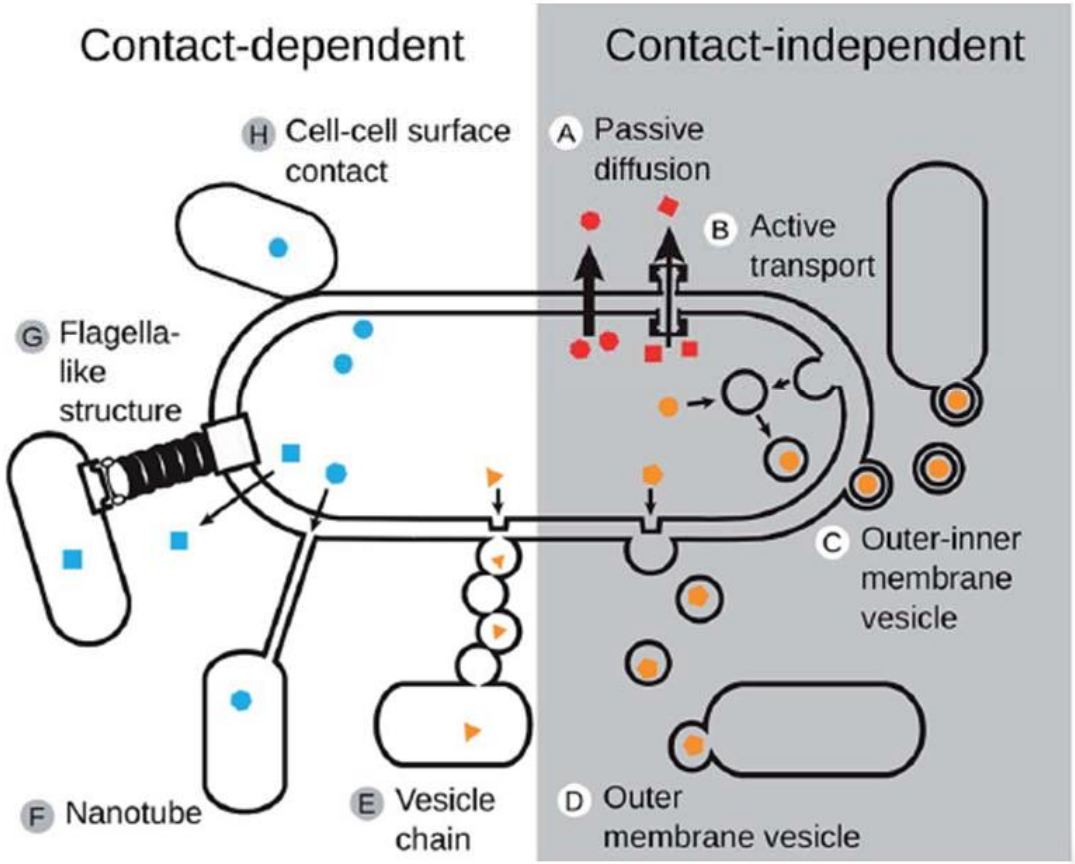
(a) *E. coli ΔtrpB Δ hisL* and *E. coli Δ his D Δ trpR* coculture after 24 h

(b) *E. coli Δ trpB Δ hisL* and *A. baylyi Δ hisD Δ trpR* coculture after 48 h



Cross-feeding of **cytoplasmic materials** via **membrane-derived** nanotubes

Mechanisms of metabolite transfer



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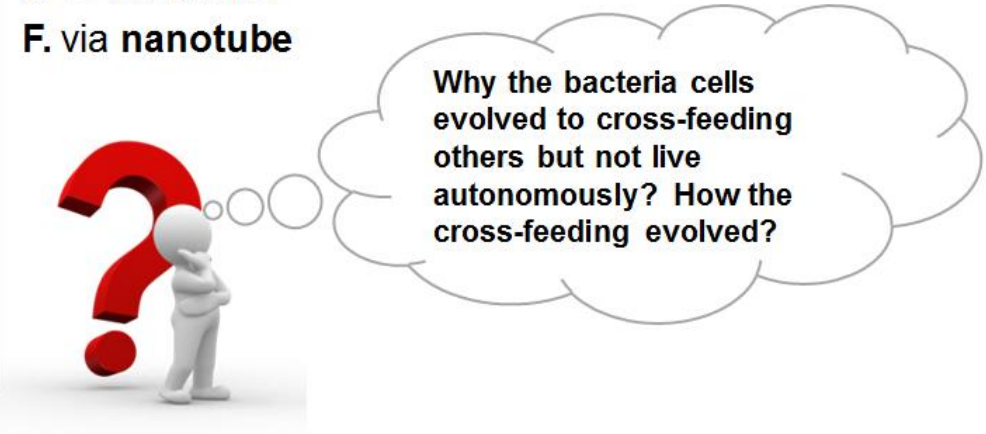
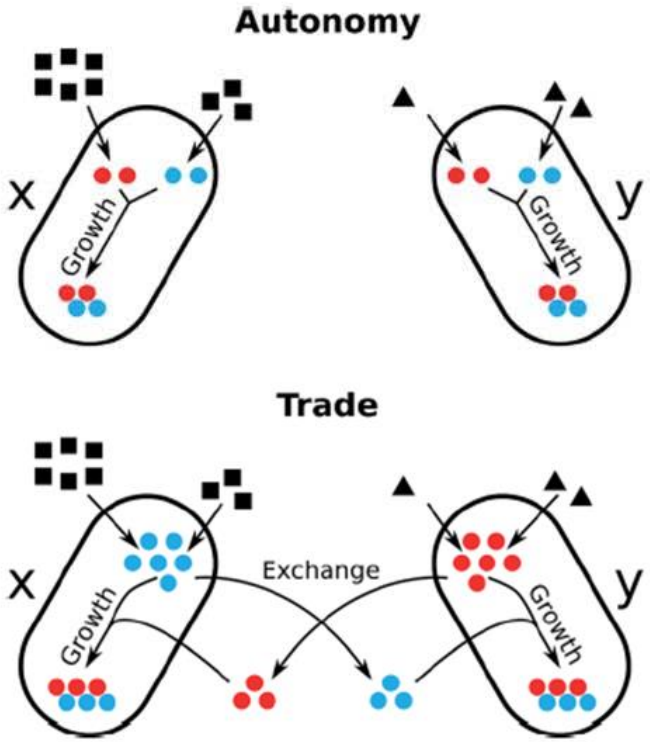


Christian Kost et al., 2018. Natural Products report

Comparative advantages theory

- David Ricardo, a British classical economist.
- In 1814, he developed this economic theory to explain how two countries could benefit from international trade.
- Industry specialization (US soybean $\rightleftharpoons$ China toy)

Economics of microbial metabolite trade

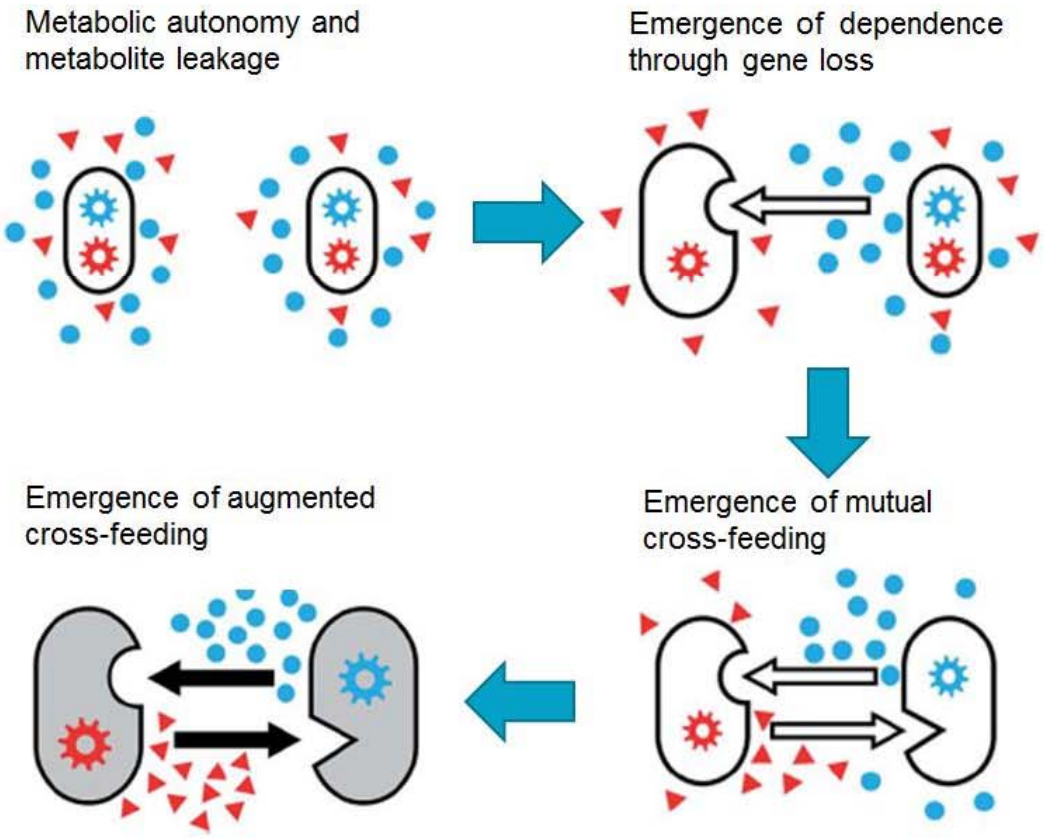


- Autonomy: bacterium x and y can produce 2 red and 2 blue metabolites for growth.
- Trade-off: if each organism specialize in the biosynthesis of the metabolite which it has the comparative advantage (x: blue, y:red) and trades half of the produced metabolites with the other organisms, each organism can dedicate 50% more of each metabolite to its growth.
- Conclusion: trade of metabolites is mutually beneficial for both organisms.

Christian Kost et al., 2018. Natural Products report

The first step of evolution

Hypothetical model



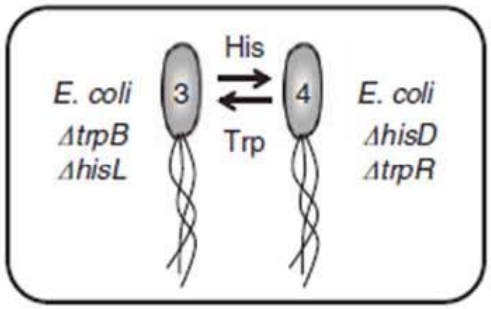
- Auxotrophies are common in microbial world.
- Bacterial genome:14 Mb (i.e. *Sorangium* cellulosum) ~ 0.16 Mb (i.e. *Candidatus Carsonella*)
- Cross-feeding in bacterial population may face challenges?

Christian Kost et al., 2018. Natural Products report

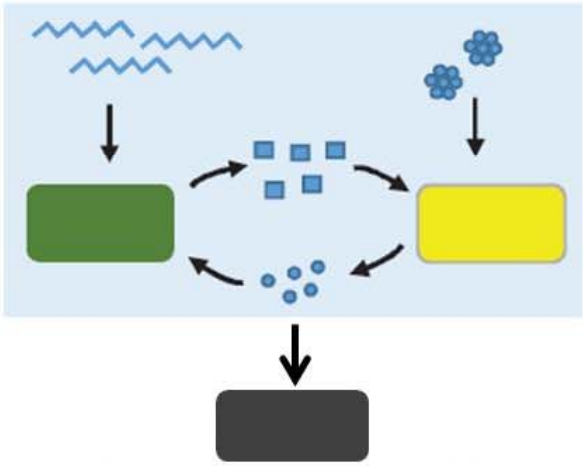
Challenges in cross-feeding

Challenge: the presence of cheaters/non-cooperator cross-feeding.

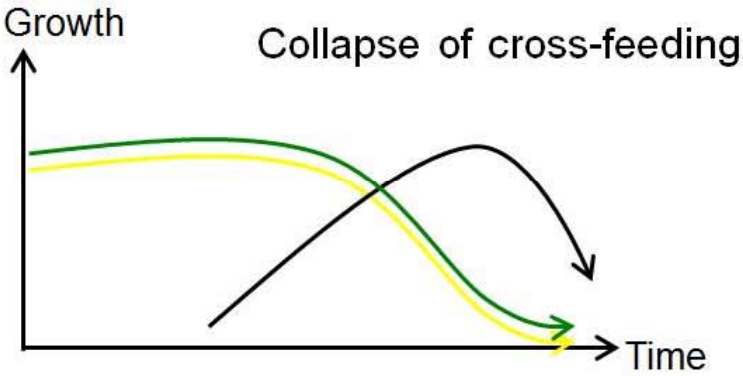
Nanotube example



Mutual cross-feeding

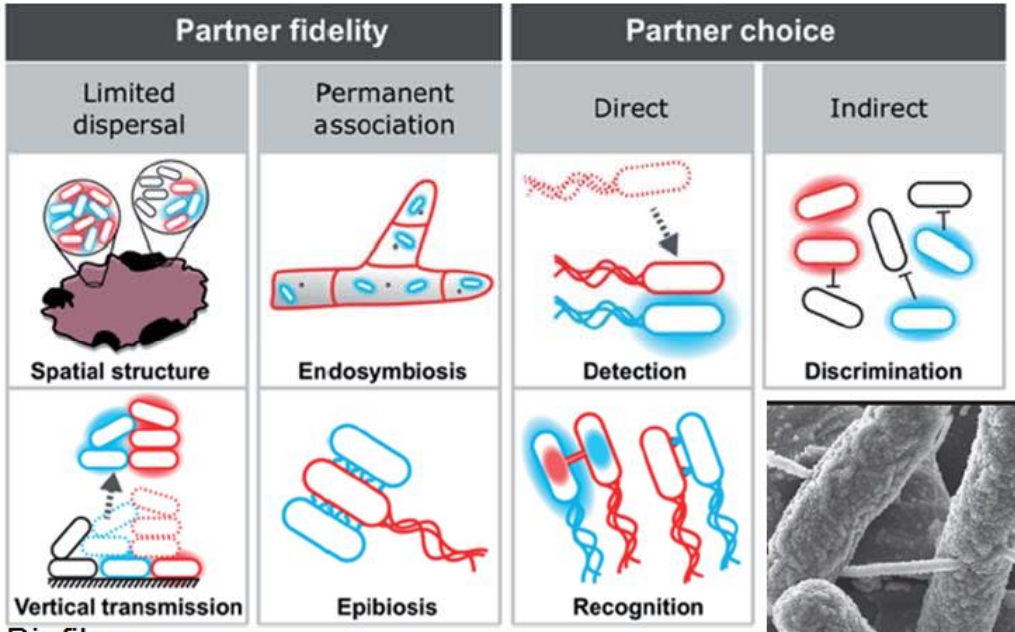


Cheaters/non-cooperator



Warren C. McNabb et al. 2019.,Frontiers in Ecology and Evolution.

Maintenance of cross-feeding



Biofilms

Nanotube example

Mechanisms promoting cooperation:

1. **Partner fidelity** (staying together): mechanisms that ensure repeated interactions among cooperators due to a physical colocalization.

2. **partner choice** (i.e. coming together): mechanisms that facilitate either the localization and subsequent association with suitable interaction partners or the antagonizing of unsuitable interaction partners.

Spatial structure, cooperation and competition in biofilms. Nature reviews,2016
Biofilms promote altruism. *Microbiology,* 2004

Christian Kost et al., 2018. Natural Products report.

Significance of cross-feeding

1. Develop strategies for **manipulating** microbial communities with human health, agricultural, and environmental implications.
2. Develop strategies for the culture of uncultured gut microbiota (the **unculturability** of most gut bacterial species).
3. Metabolic cross-feeding allows a gut microbial community to overcome detrimental diets and alter host behavior.

   (Carlos Ribeiro et al. BioRxiv, 2019)
4. Cross-feeding modulates **antibiotic tolerance** in bacterial communities. (WR. Harcombe et al., ISME, 2018.)
5. Cross-feeding modulates the rate and mechanism of **antibiotic resistance**. **(**WR. Harcombe et al. BioRxiv, 2019)

In summary

Metabolic Cross-feeding

- Molecular mechanism: passive diffusion, active transport, OMVs, nanotubes…
- Evolution: Metabolites leakage → Metabolites trade → Gene loss
- Maintenance
  - Partner fidelity
  - Partner choice

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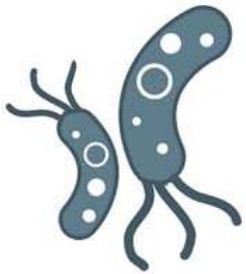
Significance

- Gut microbiota modulation
- Gut bacteria culturability
- Environment tolerance
- Antibiotic resistance



Thank you