

# Metabolons and hyperstructures in cell metabolism and signaling

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- 1 Introduction
- 2 Simulator description
- 3 Virtual experiments
- 4 Results
- 5 Conclusion



# Metabolons and Hyperstructures

- Metabolons: group of enzymes
  - With or without channelling of metabolites from one enzyme to the next in the pathway
- Hyperstructures: large group of metabolons
  - High local concentration of enzymes → high local concentration of final products



# Pathways chosen

- Phosphoenolpyruvate:sugar phosphotransferase system (PTS) in *E. coli*
  - imports sugars (such as glucose) and supplies sugar phosphates to the second pathway

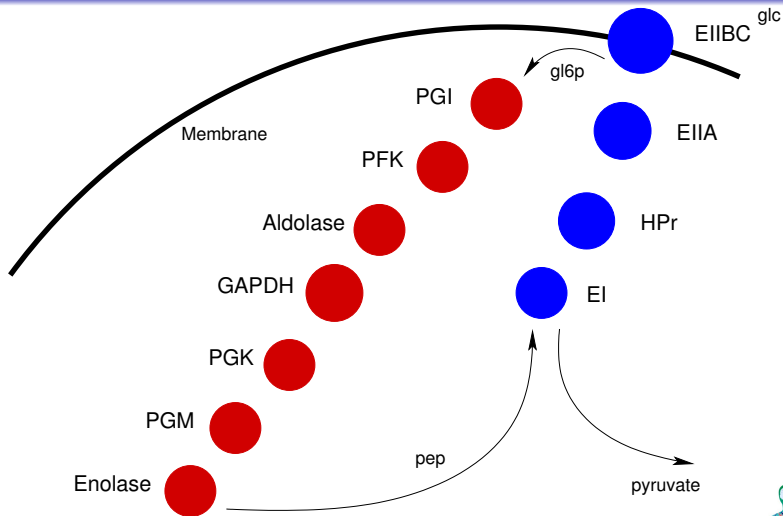


# Pathways chosen

- Phosphoenolpyruvate:sugar phosphotransferase system (PTS) in *E. coli*
  - imports sugars (such as glucose) and supplies sugar phosphates to the second pathway
- Glycolytic pathway
  - Metabolisation of glucose



# Pathways chosen



# HSIM

- Virtual bacterium simulator
  - Multi Agent System
  - 3D space surrounded by a 2D membrane
  - Each molecule is represented by an agent
- Driven by local rules between molecules
  - Mimics the biochemical reactions



# Evolution rules

4 types of rules:

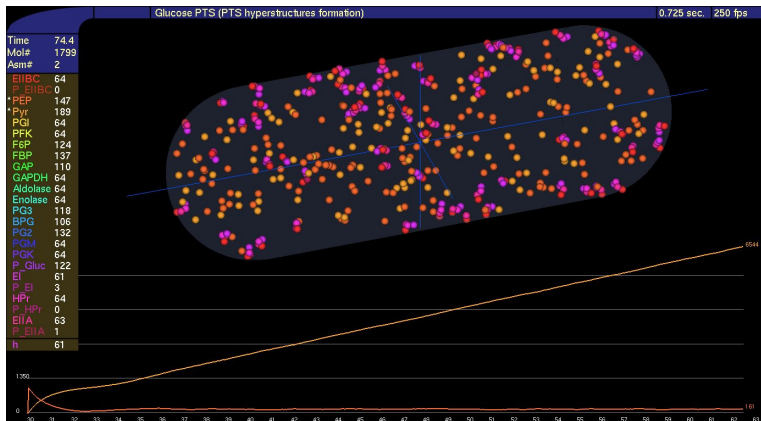
- Reaction:  $A + B \rightarrow C + D$  [Prob]
- Diffusion:  $A + \text{empty} \rightarrow \text{empty} + A$  [Prob]
- Association:  $A + B \rightarrow C * D$  [Prob]
- Dissociation:  $A * B \rightarrow C + D$  [Prob]
- Catalysis:  $A * B \rightarrow C * D$  [Prob]

Example:





# Results



- Spatial localisation of each molecule in the virtual cell
- Number of copies of each type of molecule



# Varying conditions of association

Equal numbers of enzymes (64 copies of each kind) in varying conditions of association

- 1 No association: the enzymes diffuse everywhere in the bacterium



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Equal numbers of enzymes (64 copies of each kind) in varying conditions of association

- 1 No association: the enzymes diffuse everywhere in the bacterium
- 2 Only the glycolytic pathway is assembled in metabolons
- 3 Only the PTS pathway is assembled in metabolons
- 4 Both the PTS and the glycolytic pathways are assembled in metabolons



# Influence of colocalisation

Both the pathways being assembled:

- 1 The two kind of pathways are uniformly scattered in the bacterium



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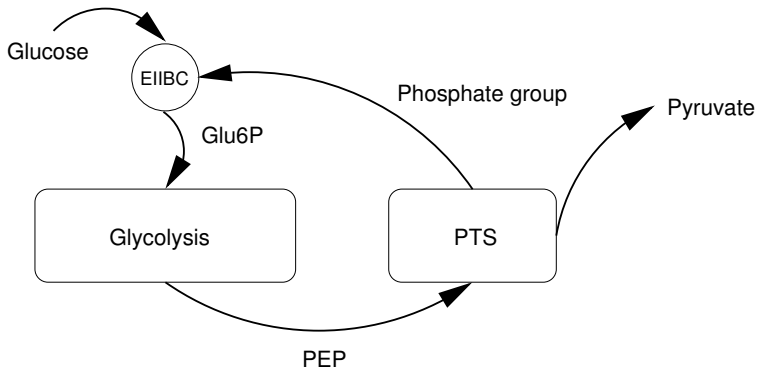
Both the pathways being assembled:

- 1 The two kind of pathways are uniformly scattered in the bacterium
- 2 They are colocalised (by sharing the membrane receptor *EIIBC<sup>glc</sup>*)
- 3 They are also attached at the other end (*Enolase* bound to *EI*)





# Positive feedback loop



- An initial presence of PEP is required to prime the system
  - Varying the number of copies of initial PEP

# 300 copies of initial PEP

Pyruvate production after 40 seconds of simulated time

No assoc.	1028
Glyc. assoc.	1059
PTS assoc.	2384
PTS+Glyc assoc.	8053

⇒ The PTS pathway is the key



# Varying the number of initial PEP

Pyruvate production after 40 seconds of simulated time

<b>Initial PEP</b>	<b>300</b>	<b>500</b>	<b>1000</b>	<b>2000</b>
No assoc.	1028	1036	1045	1076
Glyc. assoc.	1059	1096	1054	1083
PTS assoc.	2384	3990	7982	15616
PTS+Glyc assoc.	8053	13699	26752	47707



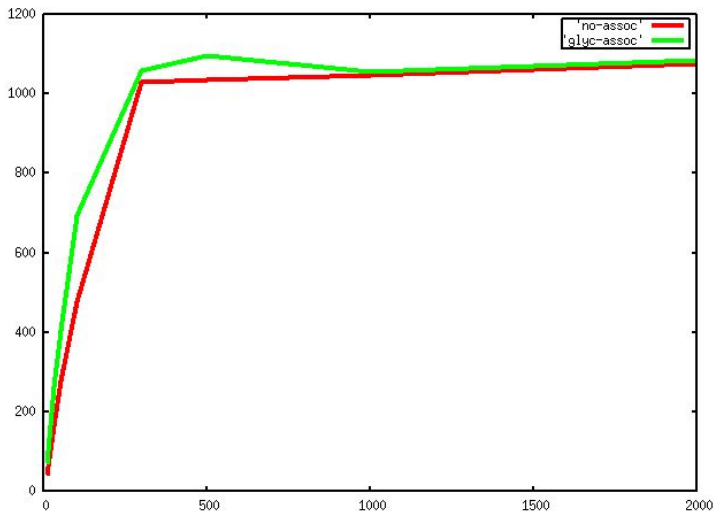
# Varying the number of initial PEP

Pyruvate production after 40 seconds of simulated time

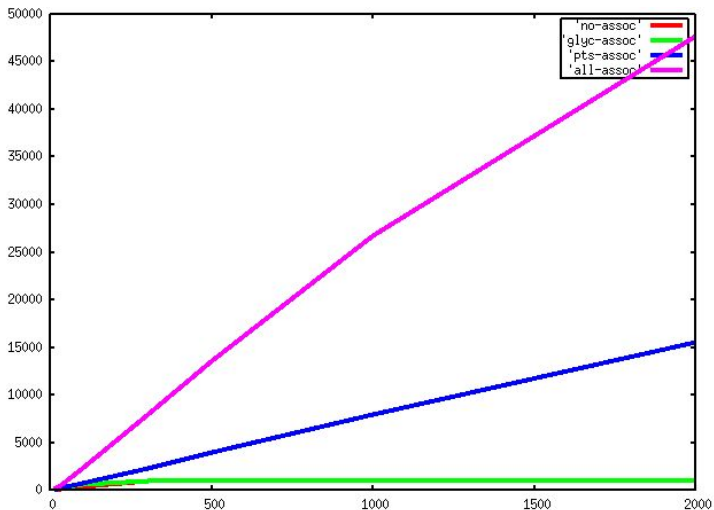
<b>Initial PEP</b>	<b>30</b>	<b>50</b>	<b>100</b>	<b>300</b>
No assoc.	167	279	479	1028
Glyc. assoc.	265	405	694	1059
PTS assoc.	245	401	819	2384
PTS+Glyc assoc.	550	981	2381	8053



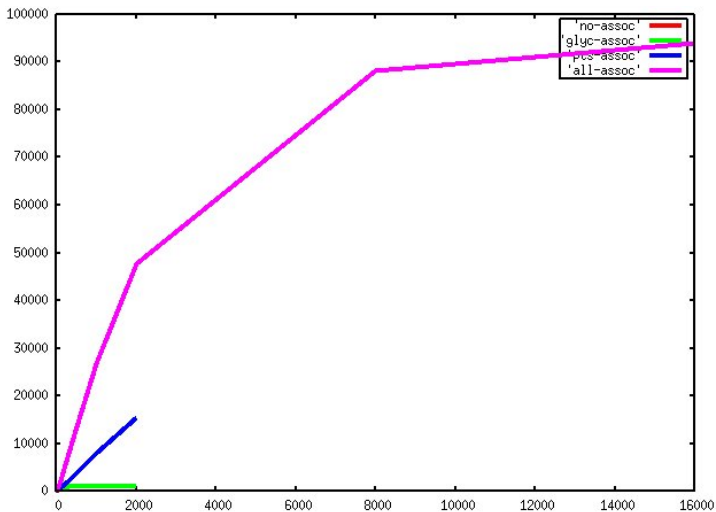
# PTS not associated



# PTS associated



# PTS associated (plateau)



# Influence of colocalisation

PTS and glycolytic pathways are assembled, each metabolon scattered in the bacterium, or assembled as a double metabolon (1 PTS + 1 Glyc) then scattered

<b>Initial PEP</b>	<b>300</b>	<b>500</b>	<b>1000</b>	<b>2000</b>
PTS+Glyc assoc.	8053	13699	26752	47707
Attached by EIIBC	8742	14129	26629	46583
Double attachment	7722	12708	23575	42847

⇒ The colocalisation of one PTS chain and one glycolytic chain has no influence on the pyruvate production rate





# Metabolons grouped in a hyperstructure

PEP production after 10 seconds (at varying rate of glucose imports) when:

- all metabolons are together in a hyperstructure (attached to a patch of EIIBC on the membrane) with and without channelling
- versus when there is no metabolon at all

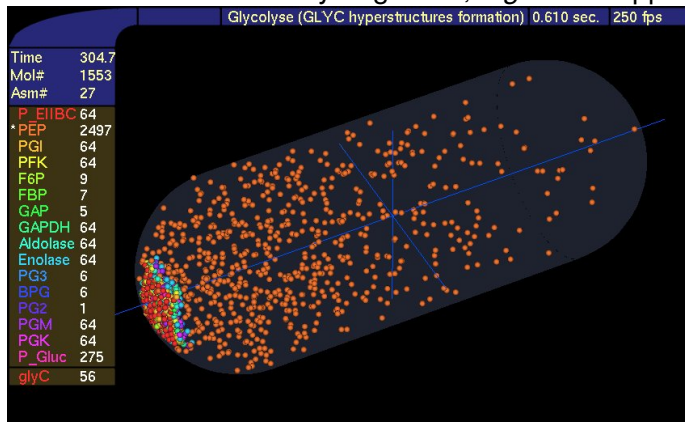
<b>Glucose per sec.</b>	<b>0.1</b>	<b>1</b>	<b>10</b>
60 sets, not in metabolons	16	216	2131
60 metabolons, no channelling	25	253	2178
60 metabolons, with channelling	55	428	4097

No advantage in terms of efficiency unless channelling is allowed (which doubled efficiency)



# Gradient of metabolites

As the production of metabolites is spatially localised, if these metabolites are uniformly degraded, a *gradient* appears.



# Conclusion

- 1 *In silico* experiments using HSIM have helped answer fundamental problems.
- 2 We have applied HSIM to the analysis of a simplified model system in steady state conditions, but it may also prove useful where parameters fluctuate.

