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Application of a dynamic metabolic flux algorithm during a temperature-induced lag phase



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ABSTRACT

In predictive microbiology, the (induced) lag-phase is a phenomenon of specific interest, as it has a large impact on the assessment of safety and quality of food products. This lag phase has been studied mostly on a macroscopic level. However, a quest for more mechanisticallybased predictive models has started, for example, through the integration of a metabolic reaction network into widely used macroscopic model structures. This multi-scale modeling approach is called dynamic metabolic flux analysis (dMFA). In this contribution, a recently developed algorithm for dMFA is used to estimate the metabolic fluxes in Escherichia coli K12 during an experimentally induced lag phase through a sudden shift in temperature. To study this phenomenon, controlled bioreactor experiments were performed: on the one hand at a fixed and optimal temperature for growth (37 °C), and on the other hand starting at 20 °C, with a sudden temperature shift to 37 °C during the exponential growth, inducing an intermediate lag phase. The evolution of biomass and metabolite concentrations was monitored during these experiments. After dMFA analysis of the gathered measurements, some interesting patterns in metabolic activity during the different growth phases are revealed. The described case study is a first practical test case to assess the capabilities of the recently developed dMFA methodology in an experimental predictive microbiology setting.

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1. Introduction

The concept of predictive microbiology entails that a detailed knowledge of the behavior, i.e., growth, survival and inactivation, of microorganisms in food products can be expressed in mathematical models, which enable an objective evaluation of the microbiological safety and quality of foods (McMeekin et al., 1997). An important phenomenon studied in predictive microbiology is the *lag phase*, which is a period in which no growth occurs as microorganisms have to adapt to a (sudden) change in environmental conditions. This can happen because of inoculation of the organism in a new medium, in which case the phase is called *initial lag*, or due to a change in one or more environmental variables, e.g., temperature or

pH, during an exponential growth phase, in which case the period is called an intermediate or induced lag phase. Because of the frequent changes in environmental conditions taking place during the production, distribution and consumption of food products, a good understanding of the lag phase is of vital importance for the assessment of microbial safety and quality of food products. Once the influence of environmental conditions on the occurrence and the length of the lag phase is determined, shelf-life of food products can be determined more accurately, and strategies can be developed to inhibit the growth of microorganisms by keeping them in this lag phase for extended periods of time.

For these reasons, the lag phase has been studied extensively in recent years in predictive food microbiology (Swinnen

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Nomenclature
List of symbols and abbreviations

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m _{ext} m _{ij}	number of extracellular metabolites average measurement for output j at time point t_i
m _i nt	number of intracellular metabolites
n	total number of reactions
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
ng	total number of spline knots over all free fluxes
n _{irr}	number of irreversible reactions
n _{meas}	number of measurements
n _{out}	number of outputs
np	number of parameters
n _{rev}	number of reversible reactions
n _{time}	number of measurement time points
n _x	number of states
ny	number of outputs
OAC	oxaloacetate
OUR	oxygen uptake rate
р	parameter vector
Phe	phenylalanine
Pro	proline
P5P	pentose-5-phosphate
PEP	phosphoenolpyruvate
PP	pentose phosphate
Pyr	pyruvate
p_u	vector of spline parameters
$\mathbf{q}_{ ext{bio}}$	biomass selection vector
R5P	ribose-5-phosphate
RID	refractive index detector
Ru5P	ribulose-5-phosphate
S	full stoichiometric matrix
S7P	seduheptulose-7-phosphate
Ser	serine succinate
Suc	
	succinyl-coenzyme A row of the stoichiometric matrix corresponding
$\mathbf{s}_{ ext{bio}}$	to the biomass pseudometabolite
Se	combined extracellular and biomass stoichio-
Je	metric matrix
S _{ext}	rows of the stoichiometric matrix correspond-
Dext	ing to extracellular metabolites
σ::	measurement standard deviation for output <i>j</i> at
σ_{ij}	time point t_i
S _{int}	rows of the stoichiometric matrix correspond-
- Inc	ing to intracellular metabolites
Т	temperature
TA	transaldolase
TCA	tricarboxylic acid
Thr	threonine
ТК	transketolase
Trp	tryptophane
Tyr	tyrosine
t ₀	initial time
t _f	final time
t _{knot}	vector containing the knot locations for each
	free flux
u	vector of free fluxes
V	reactor volume
Vm	ideal gas standard molar volume
х	vector of (concentration) states
\mathbf{x}_0	vector of initial values for the states

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