International Journal of Food Microbiology 240 (2017) 63–74

Contents lists available at ScienceDirect

International Journal of Food Microbiology

journal homepage: www.elsevier.com/locate/ijfoodmicro

Piecewise linear approximations to model the dynamics of adaptation to osmotic stress by food-borne pathogens

Aline Métris [a,*], Susie M. George [a], Delphine Ropers [b]

[a] Institute of Food Research, Norwich Research Park, Norwich NR4 7UA, UK
[b] Inria Grenoble – Rhône-Alpes Research Center, Saint Ismier, France

ARTICLE INFO

Article history:
Received 30 January 2016
Received in revised form 9 June 2016
Accepted 19 June 2016
Available online 22 June 2016

Keywords:
Systems biology
Osmotic stress
Dynamic modelling
Piecewise linear approximations

ABSTRACT

Addition of salt to food is one of the most ancient and most common methods of food preservation. However, little is known of how bacterial cells adapt to such conditions. We propose to use piecewise linear approximations to model the regulatory adaptation of *Escherichia coli* to osmotic stress. We apply the method to eight selected genes representing the functions known to be at play during osmotic adaptation. The network is centred on the general stress response factor, sigma S, and also includes a module representing the catabolic repressor CRP-cAMP. Glutamate, potassium and supercoiling are combined to represent the intracellular regulatory signal during osmotic stress induced by salt. The output is a module where growth is represented by the concentration of stable RNAs and the transcription of the osmotic gene *osmY*. The time course of gene expression of transport of osmoprotectant represented by the symporter *proP* and of the *osmY* is successfully reproduced by the network. The behaviour of the *rpoS* mutant predicted by the model is in agreement with experimental data. We discuss the application of the model to food-borne pathogens such as *Salmonella*; although the genes considered have orthologs, it seems that supercoiling is not regulated in the same way. The model is limited to a few selected genes, but the regulatory interactions are numerous and span different time scales. In addition, they seem to be condition specific: the links that are important during the transition from exponential to stationary phase are not all needed during osmotic stress. This model is one of the first steps towards modelling adaptation to stress in food safety and has scope to be extended to other genes and pathways, other stresses relevant to the food industry, and food-borne pathogens. The method offers a good compromise between systems of ordinary differential equations, which would be unmanageable because of the size of the system and for which insufficient data are available, and the more abstract Boolean methods.

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1. Introduction

Hyperosmotic stress in combination with other hurdles, such as cold chilling for beef carcasses or heat for the desiccation of chocolate, is widely used in the food industry to prevent the growth of food-borne pathogens. With an adequate secondary model, the growth rate of pathogenic *Escherichia coli* or *Salmonella* can be reliably predicted in such conditions because it is an autonomous parameter (Kocharunchitt et al., 2012; Zhou et al., 2011). During adaptation to the stress, the cultures have a phase during which the culturability of the cells decreases before resuming exponential growth (Mellefont et al., 2003; Zhou et al., 2011). It is impossible to determine reliably both the proportion of growing cells and their lag time from the population growth curves (Zhou et al., 2011), and although the introduction of stochastic elements improve the predictions, the secondary models remain uncertain (George et al., 2015). Likewise, in case of food with high water activity, secondary models describing heat inactivation diverge significantly from others (van Asselt and Zwietering, 2006). Secondary models are traditionally developed independently for different species and the parameters of the model do not relate to the genes of the bacteria nor their interaction. Whilst more and more molecular data such as gene expression and protein abundance under dynamic conditions of osmotic stress are available (Balaji et al., 2005; Finn et al., 2015; Kocharunchitt et al., 2014; Peng et al., 2014; Shabala et al., 2009; Weber and Jung, 2002; Weber et al., 2006), a model able to describe the process of adaption to osmotic stress at the molecular level has yet to be established. It could help to determine which genes are important for survival among those affected, and hence, guide anti-microbial interventions in the food chain.

* Corresponding author.
E-mail addresses: aline.metris@ifr.ac.uk (A. Métris), susie.george@ifr.ac.uk (S.M. George), delphine.ropers@inria.fr (D. Ropers).

http://dx.doi.org/10.1016/j.ijfoodmicro.2016.06.022
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At the molecular level, the adaptation to osmotic stress is characterised by exchange or accumulations of ions such as potassium and glutamate, changes in the cell envelop composition and accumulation of osmoprotectants such as trehalose (Csonka, 1989). As with many stresses relevant to the food industry, many of the genes affected are regulated by the general stress response sigma S factor, σ^S (Hengge-Aronis, 1996; Kocharunchitt et al., 2014; Weber et al., 2005), encoded by *rpoS*. Reciprocally, *rpoS* mutants show defects in resistance to osmotic stress (Shiroda et al., 2014; Stasic et al., 2012; Stoebel et al., 2009). These targets include, for instance, *osmY*, encoding a protein which is expressed transiently at the beginning of the lag time with osmotic stress induced by NaCl (Barron et al., 1986); *otsA* and *otsB* which allow the conversion of glucose into trehalose (Giaever et al., 1988). If there are some osmoprotectants in the medium, such as glycine betaine found in many environments including food (Koo and Booth, 1994), they are transported directly into the cell *via*, for instance, the symporter ProP (MacMillan et al., 1999), which is itself regulated by σ^S. In addition to being under the influence of σ^S, most of these osmotic genes are under the regulation of global regulators such as those modifying nucleotide structures: the factor for inversion stimulation, Fis, and the integration host factor, IHF, themselves regulated by σ^S (Hengge-Aronis et al., 1993). The catabolic repressor CRP-cAMP is another general regulator which has been shown to be playing a central role in osmoregulation (Balsalobre et al., 2006; Landis et al., 1999; Metris et al., 2014) as well as regulating catabolism. It can be seen from only a few genes that the interactions between them are complex, as illustrated in Fig. 1.

The complexity and the level of detail available for a biological system to be modelled constrain the choice of the mathematical formalism. If the parameters are known or can be determined, the system can be described by a set of ordinary differential equations or stochastic master equations to name but a few (Szallasi et al., 2006). Often, the experimental setups are incomparable or incomplete, leading to a lack of quantitative information on parameters and concentration variables. Given the impossibility to quantitatively describe biological systems in these cases, qualitative formalisms have been developed that account for essential dynamical properties of the system, such as the Boolean network models or the piecewise linear (PL) models. The latter captures the regulatory effects by means of step functions that change their value at threshold concentrations of the regulatory proteins. The step functions approximate the sigmoidal response functions often occurring in the cooperative regulation of gene expression (de Jong and Ropers, 2006). The resulting models provide a coarse-grained description of the network behaviour, while preserving its essential dynamical properties (Ropers et al., 2011). So far, this formalism has been used to analyse the functioning of gene regulatory networks in various microorganisms, from yeast to pathogenic bacteria (de Jong et al., 2004; Monteiro et al., 2011; Ropers et al., 2006; Sepulchre et al., 2007; Viretta and Fussenegger, 2004). In this study we propose a model of *E. coli* dynamic response to osmotic stress induced by NaCl with piecewise linear approximations. We discuss the assumptions of the model and how it could be expanded and transferred to food pathogens.

2. Materials and methods

2.1. Piecewise linear modelling and simulation

We describe briefly below the principles behind PL models of a biological system, illustrating them with concrete examples from the osmotic stress network in Fig. 1 (see the accompanying data file for additional information (Ropers and Metris, submitted for publication)). The development of the PL model follows Batt et al. (2012) and is partly based on previous work (Batt et al., 2005; de Jong et al., 2004; Ropers et al., 2011, 2006).

2.1.1. Derivation of model equations

We introduce seven state variables, each corresponding to the concentration of a protein or RNA (Fis, IHF, OtsAB, ProP, RpoS, OsmY, and stable RNAs), and one input variable denoting the NaCl concentration and thus, the osmotic stress signal. Protein synthesis is modelled in one step, by aggregating transcription and translation in a single reaction. We illustrate how the model equations are established with IHF and RpoS.

The time derivative of each variable is equal to the difference between the synthesis rate of the protein (or RNA) and its degradation rate. In the case of the σ^S-dependent expression of IHF, for example, the PL equation is:

$$\frac{d}{dt}IHF = k^2_{ihf} s^+(RpoS, t_{rpoS}) - g_{ihf} IHF,$$

where IHF is the concentration of protein IHF, k^2_{ihf} its maximal synthesis rate and g_{ihf}, its degradation rate constant. RpoS is the concentration of

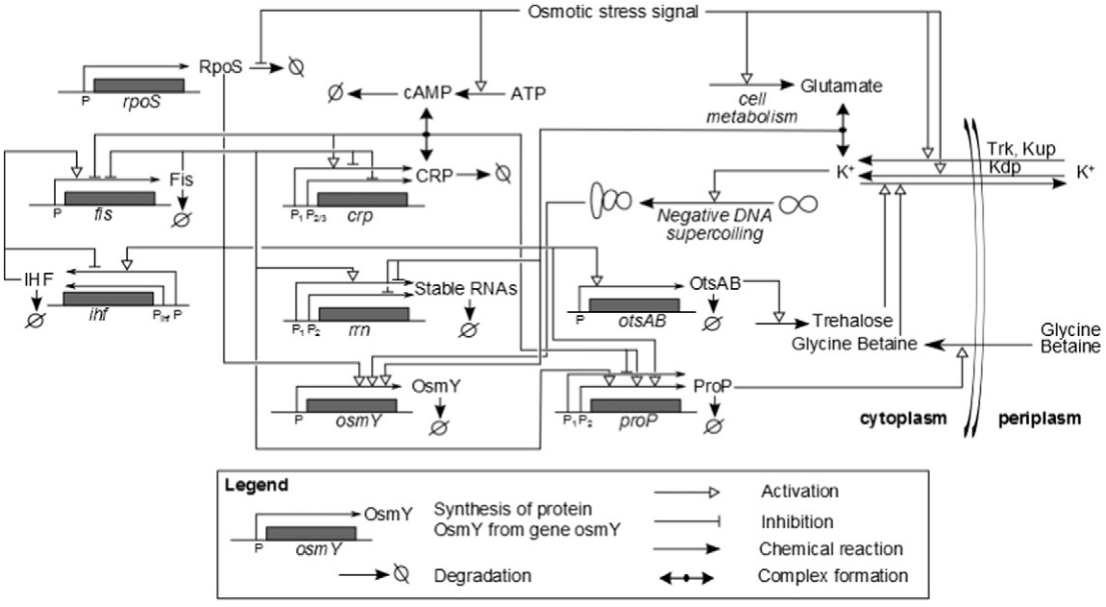

Fig. 1. Network of key genes, proteins, and regulatory interactions involved in the osmotic stress response network in *Escherichia coli*. The graphical conventions are explained in the legend.

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