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Ghjuvan Micaelu Grimaud, Francis Mairet, Antoine Sciandra, Olivier Bernard. Modeling the temperature effect on the specific growth rate of phytoplankton: a review. *Reviews in Environmental Science and Bio/technology*, 2017, 10.1007/s11157-017-9443-0. hal-01576871

**HAL Id: hal-01576871**

**<https://inria.hal.science/hal-01576871v1>**

Submitted on 24 Aug 2017

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# Modeling the temperature effect on the specific growth rate of phytoplankton: a review

Ghjuvan Micaelu Grimaud · Francis Mairet ·  
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Received: date / Accepted: date

**Abstract** Phytoplankton are key components of ecosystems. Their growth is deeply influenced by temperature. In a context of global change, it is important to precisely estimate the impact of temperature on these organisms at different spatial and temporal scales. Here, we review the existing deterministic models used to represent the effect of temperature on microbial growth that can be applied to phytoplankton. We first describe and provide a brief mathematical analysis of the models used in constant conditions to reproduce the thermal growth curve. We present the mechanistic assumptions concerning the effect of temperature on the cell growth and mortality, and discuss their limits. The coupling effect of temperature and other environmental factors such as light are then shown. Finally, we introduce the models taking into account the acclimation needed to thrive with temperature variations. The need for new thermal models, coupled with experimental validation, is argued.

**Keywords** Temperature growth models, thermal growth curve, protein thermal stability, phytoplankton, microalgae, cyanobacteria

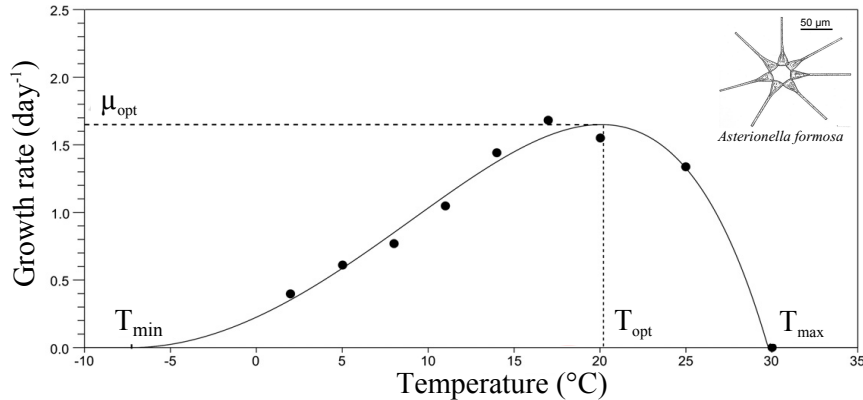
## 1 Introduction

1 Recent estimations predict a global temperature increase of 1°C to 5°C by the year 2100 (Rogelj  
2 et al, 2012). In this context, the microbial communities, either terrestrial or aquatic, are expected  
3 to be deeply impacted (Frey et al, 2013; Vezzulli et al, 2012; Thomas et al, 2012). Unicellular  
4 organisms are ectotherms and cannot regulate their temperature. They are thus particularly sensi-  
5 tive to temperature, which controls cellular metabolism by affecting enzymatic activity (Privalov,  
6 1979; Kingsolver, 2009) and stability (Privalov, 1979; Danson et al, 1996; Eijsink et al, 2005).  
7 Microorganisms play a key ecological role since they are involved in most of the biogeochemical  
8 fluxes (Paul, 2014; Fuhrman et al, 2015). Especially, the autotrophic unicellular organisms (*i.e.*  
9 phytoplankton) are the basis of trophic chains in the majority of ecological systems (Field et al,  
10 1998). Modeling the effect of temperature on phytoplankton physiology and cellular metabolism is  
11 thus crucial for better predicting ecosystems evolution in a changing environment.

12 In balanced growth conditions, the net growth rate of every microorganism as a function of  
13 temperature is an asymmetric curve (see fig. 1) called the thermal growth curve or the thermal  
14 reaction norm (Kingsolver, 2009). The cardinal temperatures corresponding to the boundaries of  
15 thermal tolerance are defined as the minimal ( $T_{min}$ ) and maximal ( $T_{max}$ ) temperatures for growth.  
16 The temperature for which growth is maximal is called the optimal temperature ( $T_{opt}$ ). The growth  
17 rate obtained at  $T_{opt}$  is the maximal growth rate  $\mu_{opt}$ , whenever all the other factors affecting  
18 growth are non-limiting. The thermal range on which a given species can thrive is the thermal

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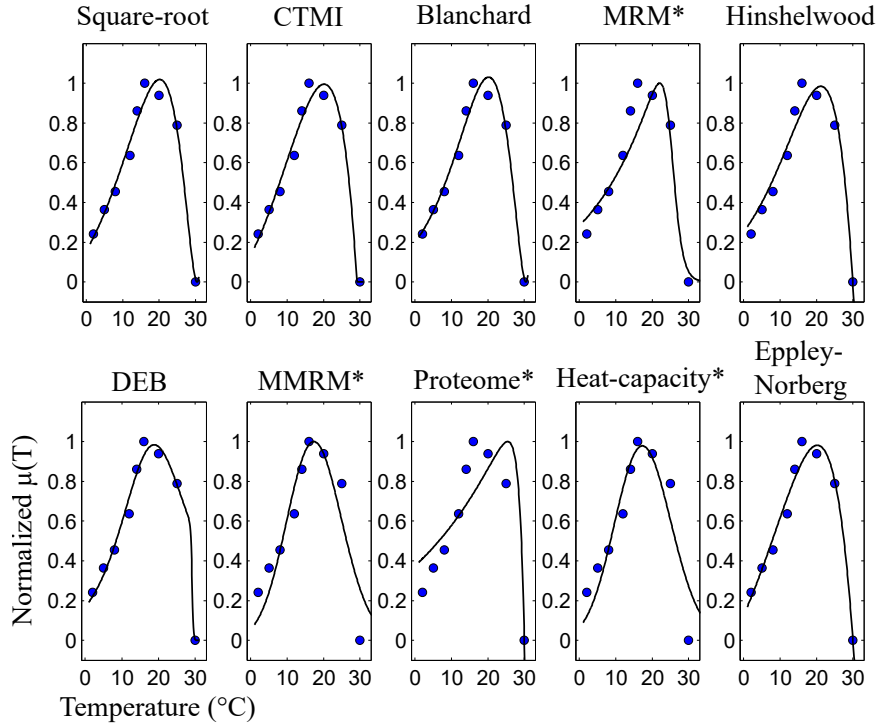
**Fig. 1** Thermal growth curve of the microalgae species *Astrionella formosa* (redrawn from Bernard and Rémond (2012)).

19 niche width (*i.e.*  $T_{max} - T_{min}$ ). The asymmetry of the growth curve results from differential effects  
 20 on physiology at low (under  $T_{opt}$ ) and high (above  $T_{opt}$ ) temperatures. At low temperatures the  
 21 rate of every enzymatic biochemical reactions are affected. At high temperatures, structure and  
 22 stability of some cellular components, such as key enzymes or membrane compounds (mainly lipids  
 23 or proteins) are denatured. The consequences on cell metabolism and integrity leads to an increase  
 24 in mortality (Serra-Maia et al, 2016). These deleterious effects depend on the time spent at high  
 25 temperature, while the ‘thermal dose’ represent the temperature damages (Holcomb et al, 1999).  
 26 The combined effects on metabolism, cell regulation mechanisms and cell integrity give the thermal  
 27 growth curve (Corkrey et al, 2014; Ghosh et al, 2016). While most of these underlying mechanisms  
 28 have not been fully elucidated, several authors have proposed macroscopic models to represent this  
 29 thermal growth curve. These simple models account for a minimum number of variables and do  
 30 not provide a detailed mechanistic description of the involved biochemical underlying phenomena.

31 The aim of this study is to summarize the existing deterministic temperature growth models  
 32 that can be used for phytoplankton, and to clarify the assumptions on the considered physiological  
 33 processes. Firstly, models in non-limited and balanced growth conditions (*i.e.* when all the cell  
 34 variables grow at the same constant rate over time) are described. The key hypotheses are explored  
 35 through the review of growth models as well as the representation of the effect of temperature on  
 36 cell mortality. Secondly, the coupling effect of temperature and other environmental factors such as  
 37 light is addressed. Thirdly, a guideline is proposed to choose a model depending on the modelling  
 38 purposes. Then, we present models taking into account temperature variations. The challenges to  
 39 design a new generation of thermal models are finally discussed.

Model	Type	# Parameters	Validation (data sets)	Cardinal temperatures	Mortality
<b>Empirical models</b>					
Square-root	E	4	29, bacteria (Ratkowsky et al, 1983)	$T_{min}$ and $T_{max}$ are explicit $T_{opt}$ is found by numerical optimization	No
CTMI	E	4	47, bacteria & yeast (Rosso et al, 1993)	Explicit	No
Blanchard	E	4	2, benthic phytoplankton (Blanchard et al, 1996)	$T_{opt}$ and $T_{max}$ are explicit $T_{min}$ is not defined	No
Bernard&Rémond	E	4	15, phytoplankton (Bernard and Rémond, 2012)	Explicit	No
Eppley-Norberg	SE	4	5, phytoplankton (Norberg, 2004)	$T_{opt} = \frac{bz - 1 + \sqrt{(w/2)^2 b^2 + 1}}{b}$ $\text{abs}(T_{max} - T_{min}) = w$	No
<b>Semi-empirical models</b>					
Arrhenius equation	SE	2	-	Not defined	No
<b>General mechanistic models</b>					
Master reaction (for eq. 19)	M	4	1, normalized, bacteria (Johnson and Lewin, 1946) and then yeast (Van Uden, 1985)	$T_{opt} = \frac{\Delta H^\ddagger / R}{\ln\left(\frac{-\Delta H^\ddagger e^{\Delta S} - \Delta H e^{\Delta S}}{\Delta H}\right)}$ $T_{min}$ and $T_{max}$ are not defined	Yes (implicit)
Hinshelwood	M	4	No	$T_{opt} = \frac{E_1 - E_2}{R \ln\left(\frac{A_1 E_1}{A_2 E_2}\right)}$ $T_{max} = \frac{E_1}{R \ln\left(\frac{A_1}{A_2}\right)}$ $T_{min} = T_{opt} \left(\frac{-E_1/\gamma}{T_{opt} - E_2/\gamma}\right)$ with $\gamma = R \ln(A_2/A_1 \epsilon (E_2 - E_1)/E_1)$	Yes (explicit)
DEB theory	M	6	No	$T_{min}$ and $T_{max}$ are not defined $T_{opt}$ is found numerically	Yes (implicit)
<b>Protein-stability based models</b>					
Modified Master reaction	M	4	230, normalized, all microorganisms (Corkrey et al, 2014)	$T_{opt} = \frac{\Delta C_p T_0 + \Delta H}{\Delta C_p + R}$ $T_{min}$ and $T_{max}$ are not defined	Yes (implicit)
Proteome based	M	2	12, normalized, bacteria (Dill et al, 2011)	$T_{min}$ and $T_{max}$ are not defined $T_{opt}$ is found numerically	Yes (implicit)
Heat capacity based	M	4	12, soil processes (Schipper et al, 2014)	$T_{min}, T_{opt}, T_{max}$ are found numerically	No

**Table 1** Synthesis of the main models for growth rate as a function of temperature (see also section 3.1). E, empirical models. M, mechanistic models. SE, semi-empirical models. ‘Validation’ corresponds to the original data sets used to develop and validate the models.



**Fig. 2** Fit of the 10 described models on the normalized thermal growth curve of *Asterionella formosa* (extracted from Bernard and Rémond (2012)). Models denoted with a \* are normalized. MRM, Master Reaction Model, MMRM, Modified Master Reaction Model.

Model	Calibration	$r^2$	AIC	BIC	# Citations
<b>Empirical models</b>					
Square-root	****	0.987	50.694	49.906	710
CTMI	*****	0.989	52.541	51.752	267
Blanchard	****	0.988	50.092	49.303	111
Bernard&Rémond	*****	0.989	52.541	51.752	77
Eppley-Norberg	****	0.988	52.064	51.275	146
<b>Semi-empirical models</b>					
Arrhenius equation	-	-	-	-	-
<b>General mechanistic models</b>					
Master reaction	***	0.944	33.443	32.457	107
Hinshelwood	**	0.945	37.946	37.157	507
DEB theory	*	0.985	33.748	32.368	-
<b>Protein-stability based models</b>					
Modified Master reaction	***	0.841	26.403	25.417	20
Proteome based	**	0.839	30.064	29.472	126
Heat capacity based	**	0.841	26.429	25.443	42

**Table 2** Comparison of the main models for growth rate as a function of temperature (see also section 3.1).  $r^2$ , |AIC| (Akaike Information Criterion) and |BIC| (Bayesian Information Criterion) are the absolute values calculated for fig. 2. ‘Calibration’ corresponds to calibration easiness, rated from 1 to 5 stars (the latter being better); calibration easiness is determined using several criteria: the associated computing time, the existence of a dedicated algorithm, the identifiability of the model, the biological meanings of the parameters. The number of citations is estimated using Google Scholar citations for the first article presenting the model.

## 2 Modeling the specific growth rate of unicellular organisms as a function of temperature: the thermal growth curve

40 In this section, we detail the existing models dedicated to the effect of temperature on the specific  
 41 growth rate of microorganisms in non-limiting conditions (see table 1 and 2 for a summary). As  
 42 discussed latter on, the specific growth rate concept (*i.e.* biomass increase per unit of time per unit  
 43 of biomass) is highly dependent on the biomass descriptor.

### 2.1 Experimental and methodological clarifications

44 The specific growth rate is defined, in batch acclimated cultures, as the specific biomass growth  
 45 rate during the exponential phase:

$$\mu(T) = \frac{1}{X} \frac{dX}{dt} = \frac{\ln(2)}{g(T)} \quad (1)$$

46 where  $T$  is a fixed temperature,  $X$  is the biomass concentration and  $g(T)$  is the generation time  
 47 (*i.e.* the time it takes to double the population size). The organisms are assumed to be in balanced  
 48 growth conditions as defined by Campbell (1957) (*i.e.* every extensive property of the growing  
 49 system increases by the same factor over a time interval), for a period long enough so that the  
 50 acclimation processes have reached their steady state.  $\mu(T)$  is commonly called the thermal growth  
 51 curve or the thermal reaction norm (Kingsolver, 2009).

52 It is important to note that in practice the thermal growth curve depends on different factors,  
 53 especially the way biomass is measured. Firstly, different biomass descriptors are commonly used,  
 54 such as cell counts, particulate organic carbon concentration (POC), total cell biovolume or optical  
 55 density. The dynamics of some descriptors is likely to be affected differentially by temperature  
 56 than, for example, the dynamics of cell concentration. In phytoplankton, the chlorophyll content  
 57 is a function of temperature (Geider, 1987), and thus the evolution of optical density results both  
 58 from the growth process and from the shift in the cellular optical properties. An ideal biomass  
 59 estimate should be proportional to the carbon mass with a temperature-independent constant.  
 60 The difficulty to compare observations from different studies is inherent to heterogeneity in the  
 61 measured descriptors.

62 Secondly, the experimental protocols are most of the time unclear on the acclimation period  
 63 preceding the growth measurement. Acclimation time can vary from one day to several weeks  
 64 (Boyd et al, 2013; Corkrey et al, 2014). In some cases, biomass evolution is probably affected  
 65 by acclimation to the new temperature. For example, some experimental protocols proceed by  
 66 gradually increasing temperature and measuring the growth rate. The main advantage is that they  
 67 provides a rapid evaluation of the temperature response, but the recorded response reflects a mix  
 68 between a transient acclimation phase and the effect of temperature on the cell metabolism. The  
 69 possible bias is however even stronger when the descriptor used is related to carbon content with  
 70 a temperature-dependent constant. For example, a too short period of acclimation results in a still  
 71 evolving biomass to chlorophyll a ratio. Therefore, if the growth rate is estimated using chlorophyll  
 72 a concentration (or turbidity) the computed growth rate will be biased.

73 The growth rate estimated from oxygen production must also be considered with care. The light  
 74 phase of photosynthesis is mainly a photochemical process and is hardly affected by temperature at  
 75 temperatures below  $T_{opt}$ . Carbon dioxide fixation in the Calvin cycle is an enzymatic process which  
 76 is highly temperature dependant. Estimating growth rate from oxygen production will thus mask  
 77 most of the temperature impact if an acclimation period has not been considered. The experimental  
 78 acclimation period at a given temperature is of major importance for the consistency of the thermal  
 79 growth curve.

80 For all these reasons, Boyd et al (2013) have developed a protocol to construct the thermal  
 81 growth curve for phytoplankton and optimize the comparability of different thermal growth curves  
 82 between different experiments and different species. This protocol specifies that:

- 83 1. the population must be acclimated to the experimental temperature for at least 4 generations  
 84 (we recommend even 7 generations),
- 85 2. the population must be kept at an exponential growth phase using semi-continuous cultures,

- 86 3. multiple biomass descriptors must be used and compared to obtain growth rates (cell counts,  
87 chlorophyll a fluorescence, etc.); we recommend to consider carbon or dry weight for biomass,  
88 4. a minimum of 6 experimental growth rates at 6 different temperatures must be obtained,  
89 5. the cultures must be carried out with three replicates,  
90 6. all the other parameters must be kept constant, if possible at optimal levels,  
91 7. the experiments with temperatures at which the cells do not grow or grow very slowly must be  
92 repeated several times,  
93 8. several strains of the same species should be compared.

## 2.2 Empirical approach to model the thermal growth curve

94 Various empirical models (*i.e.* not developed from biological assumptions) have been proposed  
95 since the 1960's to represent the thermal growth curve, but only three are still commonly used.  
96 Historically, these models have mostly been developed for food-processing industry and medical  
97 applications.

98 **The Square-Root model:** The Square-Root model was initially proposed by David Ratkowsky  
99 as an alternative to the Arrhenius model (Ratkowsky et al, 1982) (see eq. 9) and then extended to  
100 the whole biokinetic range (Ratkowsky et al, 1983):

$$\mu(T) = \left[ b \left( T - T_{min} \right) \left( 1 - e^{c(T - T_{max})} \right) \right]^2 \quad (2)$$

101 with

$$T_{min} \leq T \leq T_{max} \quad (3)$$

102 where  $T_{min}$  and  $T_{max}$  are the minimal and maximal temperatures for growth,  $b$  is the regression  
103 coefficient of the squared root growth rate plotted against temperatures below the optimal tem-  
104 perature, and  $c$  is an additional parameter to represent growth rate decrease above the optimal  
105 temperature.

106 **The CTMI model:** The CTMI (Cardinal Temperature Model with Inflexion) was developed by  
107 Lobry et al (1991) and later popularized by Rosso et al (1993):

$$\begin{cases} \mu(T) = 0 & \text{if } T < T_{min} \\ \mu(T) = \mu_{opt} \phi(T) & \text{if } T_{min} \leq T \leq T_{max} \\ \mu(T) = 0 & \text{if } T > T_{max} \end{cases} \quad (4)$$

108 with

$$\phi(T) = \frac{(T - T_{max})(T - T_{min})^2}{(T_{opt} - T_{min}) \left[ (T_{opt} - T_{min})(T - T_{opt}) - (T_{opt} - T_{max})(T_{opt} + T_{min} - 2T) \right]} \quad (5)$$

109 under the condition (Bernard and Rémond, 2012):

$$T_{opt} > \frac{T_{min} + T_{max}}{2} \quad (6)$$

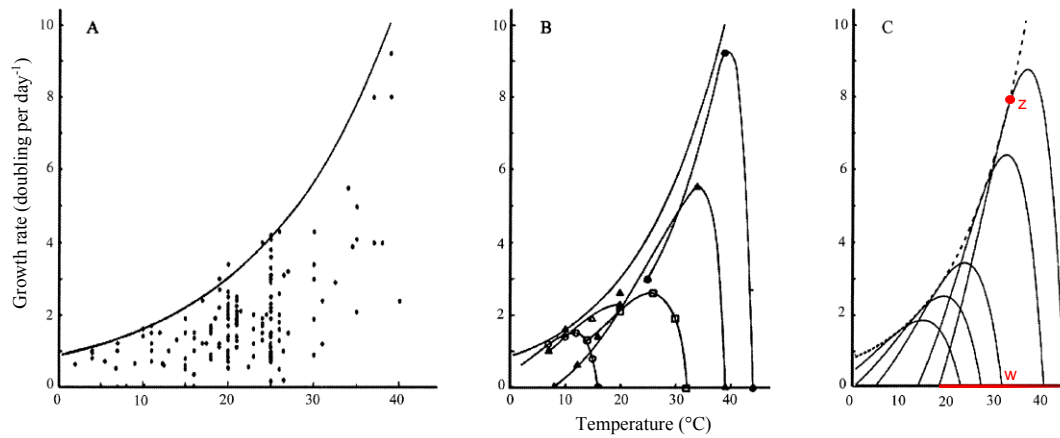
110  $T_{min}$ ,  $T_{opt}$ ,  $T_{max}$  are the minimal, optimal and maximal temperature for growth and  $\mu_{opt}$  is the  
111 growth rate at  $T_{opt}$ . The model parameters have a direct biological interpretation. The model was  
112 built for an easy calibration on experimental data.

113 **The Blanchard model:** The Blanchard model was developed by Blanchard et al (1996) to model  
114 the photosynthetic capacity of benthic phytoplankton as a function of temperature. This model  
115 can be used to represent the thermal growth curve:

$$\mu(T) = \mu_{opt} \left( \frac{T_{max} - T}{T_{max} - T_{opt}} \right)^\beta e^{-\beta(T_{opt} - T)/(T_{max} - T_{opt})} \quad (7)$$

116 with  $T \leq T_{max}$  and  $T_{opt} < T_{max}$ . Parameters  $T_{opt}$  and  $T_{max}$  correspond to the cardinal tempera-  
117 tures,  $\mu_{opt}$  is the growth rate at  $T = T_{opt}$  and  $\beta$  is a dimensionless parameter.

118 **The Eppley-Norberg model:** In 1972, Eppley (1972) reviewed the effect of temperature on  
119 phytoplankton growth in the sea by comparing different thermal growth curves for a variety of



**Fig. 3** A, Eppley envelope function with the original data points. B, 5 data sets for eukaryotic phytoplankton species. C, Eppley-Norberg plot for the 5 species (redrawn from Norberg (2004)).

120 phytoplankton species in non-limiting conditions (nearly 200 data points). Eppley (1972) deter-  
 121 mined that the maximal growth rate  $\mu_{opt}$  for each species is constrained by a virtual envelope along  
 122 the optimal temperature trait  $T_{opt}$ , the so-called ‘Eppley curve’ (see fig. 3). Eppley (1972) stated  
 123 that for any phytoplankton species growing under 40°C, ‘hotter is faster’.

124 Using Eppley’s hypothesis, Norberg (2004) developed a temperature-growth model, the ‘Eppley-  
 125 Norberg’ model:

$$\mu(T) = \left[ 1 - \left( \frac{T - z}{w} \right)^2 \right] a e^{bT} \quad (8)$$

126 where  $w$  is the thermal niche width,  $z$  is the temperature at which the growth rate is equal to  
 127 the Eppley function and is a proxy of  $T_{opt}$ ,  $a$  and  $b$  are parameters of the Eppley function. The  
 128 Eppley-Norberg model is widely used by the scientific community working on phytoplankton (*e.g.*  
 129 see the recent paper of Taucher et al (2015)).

### 130 2.3 Empirical model comparison

131 A comparison between the Square-Root model and the CTMI was made by Rosso et al (1993) and  
 132 more recently by Valik et al (2013). According to these studies, the two models fit equally well  
 133 the data. Both models are validated by Valik et al (2013) using an F-test. However, the  $b$  and  $c$   
 134 parameters of the Square-root model are correlated, whereas the CTMI parameters are not, which  
 135 allows easier parameter identification.

136 A more extensive comparison between the set of empirical models is presented on Figure 2  
 137 for *Asterionella formosa*. It turns out that most of them can successfully describe this data set,  
 138 but the fit is almost perfect for the CTMI and the Square-Root model. The CTMI proves useful  
 139 for cardinal temperatures identification since all these parameters have a biological meaning. A  
 140 guideline for choosing the most appropriate model is proposed in the discussion section.

### 141 2.4 Semi-empirical approach

142 Semi-empirical models use a combination of biological mechanisms and empirical formulations. The  
 143 very first temperature model, the Arrhenius equation, was developed in this way.



144 **The Arrhenius equation:** In the beginning of the 20<sup>th</sup> century, the work of Jacobius Van't-  
 145 Hoff and Svante Arrhenius on the effect of temperature on chemical reactions (Arrhenius, 1889)  
 146 was introduced in biology by Charles Snyder (Snyder, 1906), setting that temperature has an  
 147 exponential influence on biological reactions and then on cellular growth according to the following  
 148 equation called ‘the Arrhenius law’:

$$k(T) = Ae^{-E/(RT)} \quad (9)$$

149 where  $k(T)$  is the rate of reaction,  $R$  is the gas constant,  $A$  is called the ‘collision factor’ or the  
 150 pre-exponential part and  $E$  is the activation energy, determined empirically. The Arrhenius equa-  
 151 tion is semi-empirical, partially based on thermodynamical considerations; it can be interpreted  
 152 as the number of collisions per unit of time multiplied by the probability that a collision results  
 153 in a reaction. The Arrhenius equation is widely used to describe the temperature effect on differ-  
 154 ent biological processes, from enzyme catalysis to community activity (*e.g.* see Frauenfelder et al  
 155 (1991), Lloyd and Taylor (1994), Gillooly et al (2001)). However, it is only valid on a small range  
 156 of temperature, excluding high temperatures inhibiting growth (Slator, 1916). Arrhenius model  
 157 parameters are easy to estimate using an Arrhenius plot, by expressing  $\ln(\mu(T))$  as a function of  
 158  $1/T$ , which gives a linear relationship; parameters can thus be obtained with a linear regression.  
 159 The Arrhenius model allows good representations of growth rates at low temperatures, but some  
 160 Arrhenius plot does not give straight lines, indicating for example that  $E$  can vary with  $T$ . More-  
 161 over, the Arrhenius model cannot represent the decreasing part of the thermal growth curve, *e.g.*  
 162 when temperature causes cell death. Arrhenius equation can be conveniently reformulated as:

$$k(T) = k_r e^{T_A/T_r - T_A/T} \quad (10)$$

163 where  $T_r$  is a reference temperature,  $T_A$  is the Arrhenius temperature (*i.e.* slope of the straight  
 164 line of the Arrhenius plot) and  $k_r$  is the reaction rate at  $T_r$ .

## 165 2.5 Mechanistic approach

166 The empirical models are convenient to identify the main characteristics of the thermal growth  
 167 curve. However, the mechanistic approach aims to represent the thermal growth curve as a result of  
 168 the inherent physiological processes. These models are mostly based on the Arrhenius formulation,  
 169 but also on the Eyring equation. In addition to their explanatory role, because their parameters  
 170 have thermodynamical meanings, it is possible to extract thermodynamical informations from the  
 171 thermal growth curve only.

### 172 2.5.1 General models based on the Arrhenius and Eyring formulations

173 **The Eyring equation and the Transition-State theory:** this theory stipulates that, during a  
 174 chemical reaction, there exists an intermediate form between the reactants and the products (*e.g.*  
 175 the native and denatured protein and enzyme) which is in rapid equilibrium with the reactants  
 176 (Eyring, 1935):

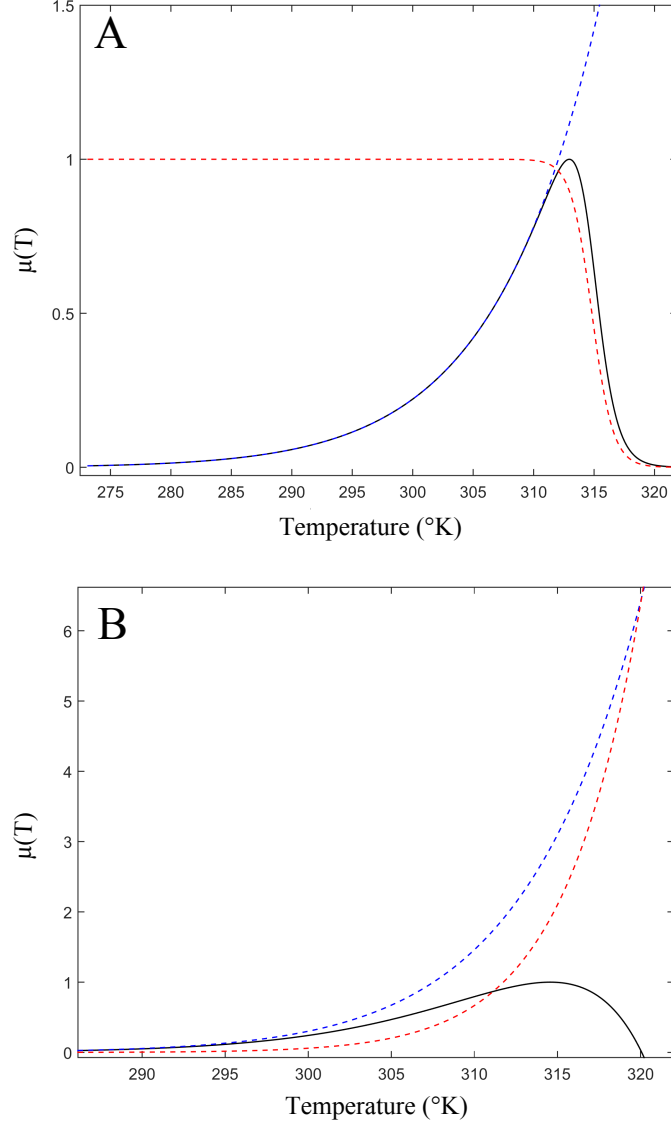


177 where, in this example,  $P_f$  and  $P_u$  are the fraction of native and denatured proteins, respectively,  
 178 and  $TS$  is the transition state. The Eyring equation, roughly similar to the Arrhenius law, was  
 179 nonetheless based on these pure mechanistic considerations and reads (Eyring, 1935):

$$k(T) = \frac{K_B T}{h} e^{\Delta S^\ddagger/R} e^{-\Delta H^\ddagger/(RT)} \quad (12)$$

180 where  $K_B$  is the Boltzmann constant,  $h$  is the Planck’s constant. The parameters  $\Delta S^\ddagger$  and  $\Delta H^\ddagger$   
 181 correspond to the entropy and enthalpy of activation for the transition state.

182 **The master reaction model:** In 1946, Johnson and Lewin noticed that cultures of *Escherichia*  
 183 *coli* exposed to 45°C during a long time ceased to grow, but grew exponentially again when replaced  
 184 at 37°C. The longer the cultures were exposed to the high temperature, the lower was the growth  
 185 rate at 37°C. However, there was no sign of viability loss. They concluded that cells endured  
 186 reversible damage, particularly protein denaturation. They considered a simple case where a single  
 187 reaction controlled by one master enzyme  $E_n$  limits growth (with no substrate limitation):



**Fig. 4** Illustration of the master reaction model (A) and of the Hinshelwood model (B). The black lines correspond to  $\mu(T)$ , the blue dashed lines corresponds to  $CTe^{-\Delta H_A^\ddagger/(RT)}$  (A) and to  $f_1(T)$  (B), the red dashed line corresponds to  $P(T)$  (A) and to  $f_2(T)$  (B).

$$\mu(T) = cTE_n e^{-\Delta H_A^\ddagger/(RT)} e^{\Delta S_A^\ddagger/R} \quad (13)$$

188 where  $c$  is a constant given by the Eyring formulation (Eyring, 1935),  $\Delta H_A^\ddagger$  is the enthalpy of  
 189 activation (enthalpy difference between the transition complex and the active form) and  $\Delta S_A^\ddagger$  is  
 190 the entropy of activation.

191 The enzyme goes from a native, active form  $E_n$  to a reversibly denatured, inactive form  $E_d$ :



192 The chemical equilibrium is defined as:

$$K = k_1/k_2 = E_d/E_n = e^{-\Delta H/(RT) + \Delta S/R} \quad (15)$$

193 where  $\Delta H$  is the enthalpy difference between the active form and the inactive form,  $\Delta S$  is the  
 194 entropy difference. If  $E_0$  is the total amount of enzyme,  $E_0 = E_n + E_d$ . It follows that:

$$E_n = \frac{E_0}{1 + K} = \frac{E_0}{1 + e^{-\Delta H/(RT) + \Delta S/R}} \quad (16)$$

195 Then, by posing  $C = ce^{\Delta S_A^\ddagger/R} E_0$  and replacing  $E_n$  by eq. 16 in eq. 13, Johnson and Lewin obtained  
 196 the master reaction model (see fig. 4 A):

$$\mu(T) = CT e^{-\Delta H_A^\ddagger/(RT)} \cdot \underbrace{\frac{1}{1 + e^{-\Delta G(T)/(RT)}}}_{P(T)} \quad (17)$$

197 where  $P(T)$  is the probability that the enzyme is in its native state and  $\Delta G(T)$  is the Gibbs free  
 198 energy change:

$$\Delta G(T) = \Delta H - T\Delta S \quad (18)$$

199 However, the master reaction model assumes that  $\Delta G$  is temperature independent. An other version  
 200 of eq.17 exists, where the exponential part does not follow an Eyring formulation but rather an  
 201 Arrhenius one, which is relevant in the case of reactions with high activation energy like protein  
 202 denaturation (Bischof and He, 2005):

$$\mu(T) = C e^{-\Delta H_A^\ddagger/(RT)} \cdot \frac{1}{1 + e^{-\Delta G(T)/(RT)}} \quad (19)$$

203 It is worth noting that this equation here simplifies the calculation of the cardinal temperature  
 204  $T_{opt}$  and is supposed to have little influence on the model fit and behavior (see table 1 and 2).

205 **The Hinshelwood model:** In 1945, Sir Norman Hinshelwood proposed a rather simple model in  
 206 which the temperature-dependent growth rate is just the difference between a synthesis rate  $f_1(T)$   
 207 and a degenerative rate  $f_2(T)$  (Hinshelwood, 1945) (see fig. 4 B):

$$\mu(T) = \underbrace{A_1 e^{-E_1/(RT)}}_{f_1(T)} - \underbrace{A_2 e^{-E_2/(RT)}}_{f_2(T)} \quad (20)$$

208 where  $A_1$  and  $A_2$  are related to entropy and  $E_1$  and  $E_2$  are related to enthalpy. Hinshelwood  
 209 believed that the function  $f_2(T)$ , which causes the ‘catastrophic decline to zero’(Hinshelwood,  
 210 1945), represents protein denaturation. He argued that the model only works if  $E_2$  is higher than  $E_1$ ,  
 211 because the degenerative process represented by  $f_2(T)$  must be sudden. Since protein denaturation  
 212 possesses a high activation energy, it is a good candidate for driving the process. Moreover,  $A_2$   
 213 (corresponding to entropy) also has to be quite high. Thus, the ‘activated state must be highly  
 214 disordered compared with the initial state’ which ‘results in an easy transition to the activated state  
 215 in spite of the large amount of energy which has to be taken up to reach it’(Hinshelwood, 1945).  
 216 Precisely, protein denaturation leads from a highly ordered state to an highly disordered state and  
 217 is therefore associated with a large entropy increase. From the Hinshelwood model, after some  
 218 mathematical manipulations, it is possible to express  $T_{min}$ ,  $T_{opt}$ ,  $T_{max}$  (see table 1).

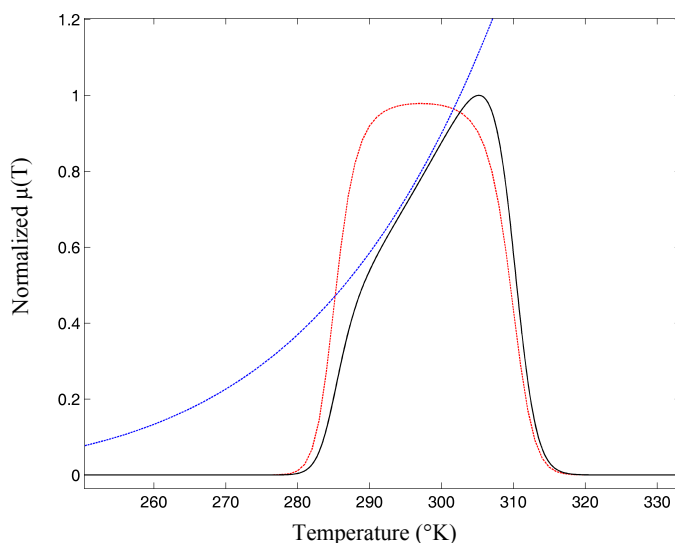
219 **The DEB theory approach:** In the Dynamics Budget Theory, the effect of temperature on  
 220 population growth is taken into account using a modified Master Reaction model (Kooijman,  
 221 2010), where all the temperature-dependent functions are Arrhenius modified equations:

$$\mu(T) = \frac{k_1 e^{T_A/T_1 - T_A/T}}{\underbrace{1 + e^{T_{AL}/T - T_{AL}/T_L} + e^{T_{AH}/T_H - T_{AH}/T}}_{f_D}} \quad (21)$$

222 where  $T_L$  and  $T_H$  are related to cold and hot denaturation (lower and upper boundaries),  $T_{AL}$  and  
 223  $T_{AH}$  are the Arrhenius temperatures (*i.e.* the slope of the straight line of the Arrhenius plot at  
 224 low and high temperatures respectively, see eq. 10). The ratio  $f_D^{-1}$  corresponds to the fraction of  
 225 enzyme in its native state. This model therefore also accounts for cold denaturation, contrary to  
 226 the Master Reaction model.

### 227 2.5.2 The protein thermal stability hypothesis

228 In addition to the temperature-dependent enzyme activity, protein thermal stability plays a key role  
 229 in the microbial thermal growth curve (Johnson and Lewin, 1946; Rosenberg et al, 1971; Zeldovich  
 230 et al, 2007; Pena et al, 2010). If temperature increases, certain proteins become first inactive and  
 231 then denatured. Especially, at high temperatures ( $T > T_{opt}$ ), this phenomenon occurs for many  
 232 proteins and causes a growth rate decrease. In line with the master reaction model, some models



**Fig. 5** The modified master reaction model plot for a microbial species (black line) with activation function (blue dashed line) and protein denaturation probability  $P(T)$  (red dashed line).

233 include additional assumptions about protein thermal stability and its consequences on growth,  
 234 assuming that proteins are the key factors controlling thermal growth curves.

235 **The modified master reaction model:** The master reaction model assumes that  $\Delta G$ , the  
 236 Gibbs free energy difference between the native and denatured protein, is temperature independent.  
 237 Based on Murphy et al (1990) work, Ross (1993) and then Ratkowsky et al (2005) remarked that  
 238  $\Delta G$  should vary with  $T$  in eq. 17 following eq. 18. Moreover, Murphy et al (1990) showed that  
 239 globular proteins (including enzymes) share common thermodynamic properties. For any protein,  
 240 the denaturation enthalpy change ( $\Delta H$ ) and the denaturation entropy change ( $\Delta S$ ), normalized to  
 241 the number of amino-acids residues of this protein, both converge to a fixed value  $\Delta H^*$  and  $\Delta S^*$   
 242 at  $T_H^*$  and  $T_S^*$  respectively (Privalov, 1979). The reason for such a temperature convergence is still  
 243 unclear. Nonetheless, it has been shown that, at  $T_H^*$  and  $T_S^*$ , the hydrophobic contribution to  $\Delta H$   
 244 and  $\Delta S$  approaches zero (Robertson and Murphy, 1997). Using the heat capacity thermodynamic  
 245 parameter  $C_p$ , Murphy et al (1990) stated that  $\Delta H$  and  $\Delta S$  can be expressed as a function of the  
 246 heat capacity change  $\Delta C_p$ :

$$\Delta H = \Delta H^* + \Delta C_p(T - T_H^*) \quad (22)$$

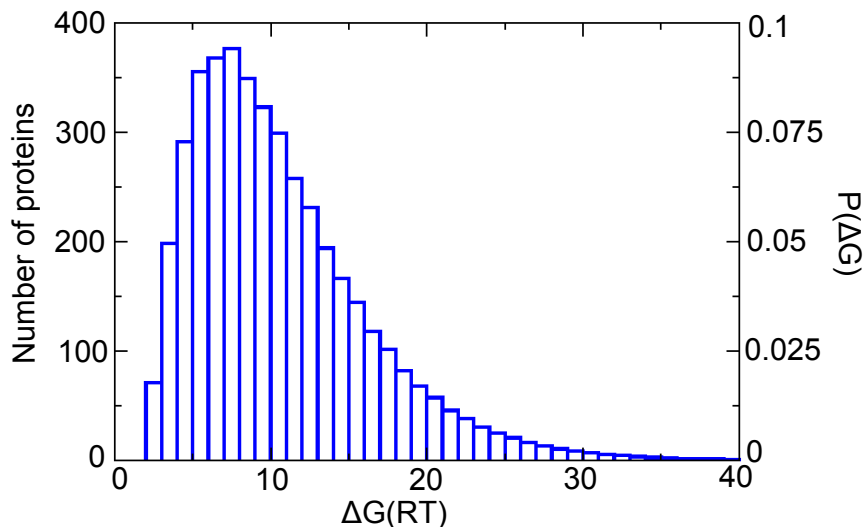
$$\Delta S = \Delta S^* + \Delta C_p \ln(T/T_S^*) \quad (23)$$

247 where  $\Delta H^*$  is the enthalpy change per mol of amino-acid residue of the enzyme at  $T_H^*$ ,  $\Delta S^*$  is  
 248 the entropy change per mol of amino-acid residue of the enzyme at  $T_S^*$ ,  $\Delta C_p$  is the heat capacity  
 249 difference between the native and denatured protein,  $T_H^*$  is the temperature at which the contri-  
 250 bution of  $\Delta C_p$  to enthalpy is zero and  $T_S^*$  is the temperature at which the contribution of  $\Delta C_p$   
 251 to entropy is zero. The heat capacity change  $\Delta C_p$  is constant for a given protein (Privalov and  
 252 Khechinashvili, 1974). Using eq. 22 and eq. 23, the Gibbs free energy of protein denaturation (*i.e.*  
 253 the protein thermal stability) is (fig. 5):

$$\Delta G(T) = n \left[ \Delta H^* - T \Delta S^* + \overbrace{\Delta C_p [(T - T_H^*) - T \ln(T/T_S^*)]}^{\Delta G_{hydro}} \right] \quad (24)$$

254 where  $n$  is the number of amino-acid residues in the master enzyme and  $\Delta G_{hydro}$  is the hydrophobic  
 255 contribution to the free energy change. Eq. 24 describes protein thermal stability in terms of  
 256 hydrophobic contribution of apolar compounds.

257 Ross (1993) and Ratkowsky et al (2005) proposed to replace  $\Delta G$  by eq. 24 in eq. 17 (forming the  
 258 modified master reaction model). Because  $T_H^*$ ,  $T_S^*$  and  $\Delta S^*$  are considered as universal constant  
 259 for globular proteins (Murphy and Gill, 1991), the modified master reaction model has 5 tunable



**Fig. 6** Gibbs free energy distribution of *Escherichia coli* proteome at 37°C (adapted from Ghosh and Dill (2010)).

parameters (fig. 5). As a validation, Ratkowsky et al (2005) fitted the model on 35 bacterial strains normalized data sets obtained in non-limiting conditions. Their main conclusion points towards the crucial role played by a single master enzyme whose thermal sensitivity is driven by hydrophobic interactions.

Corkrey et al (2014) extended the modified master reaction model to unicellular and multicellular eukaryotes. They considered  $\Delta H^*$  as a universal constant as well, reducing the model parameters to 4. They fitted the model on 230 strains normalized data sets covering a range of 124°C. Their principal conclusion states that the model is able to find coherent protein thermodynamics parameters with only net growth rates data (*i.e.* growth rate versus temperature). Hyperthermophiles proteins seem to be more widely robust. Moreover, they found several links between thermodynamic parameters, for example between  $T_{opt}$  and  $\Delta C_p$  (enzyme stability), and between  $T_{opt}$  and  $\Delta H^\ddagger$  (enzyme activity). However, they did not provide further explanations. They finally speculate on the nature of the single limiting reaction. They assume that if a single reaction (and not several) is rate limiting, then it should be linked to the protein unfolding and re-folding process. They particularly focus on the role of chaperones proteins responsible for *de novo* folding.

**The proteome-scale approach:** Zeldovich et al (2007) proposed that the whole proteome plays a role in microbial thermal sensitivity. Resuming this idea, Chen and Shakhnovich (2010) considered that each important protein  $i$  has its own Gibbs free energy of denaturation  $\Delta G_i$ . The growth rate of a microbe becomes dependent of the stability of each protein, and the thermal denaturation of several proteins causes a bottleneck effect on growth:

$$\mu(T) = CT e^{-\Delta H^\ddagger/(RT)} \cdot \frac{1}{\prod_i^{N_p} (1 + e^{-\Delta G_i(T)/(RT)}} \quad (25)$$

where  $N_p$  is the number of proteins. According to Zeldovich et al (2007), the proteome can be described in protein stability distribution thanks to a dedicated probability function of the Gibbs free energy,  $P(\Delta G)$  (see fig.6). By taking the natural logarithm of eq. 25, Chen and Shakhnovich (2010) expressed the growth rate as:

$$\ln(\mu(T)) = \ln(CT) - \Delta H^\ddagger/(RT) - \sum_{i=1}^{N_p} \ln(1 + e^{-\Delta G_i/(RT)}) \quad (26)$$

that is, by integrating the resulting equation over the whole  $P(\Delta G)$  distribution range and by averaging over the proteome:

$$\ln(\mu(T)) \simeq \ln(CT) - \Delta H^\ddagger/(RT) - N_p \int_0^L \ln\left(1 + e^{-\Delta G/(RT)}\right) P(\Delta G) d\Delta G \quad (27)$$

287 where  $L$  is the maximum value of  $\Delta G$  (for example  $L = 40$  in fig. 6).  $N_p$  can be reduced to the  
 288 number of the only important proteins. According to Sawle and Ghosh (2011) and Ghosh and Dill  
 289 (2010),  $\Delta G$  can be expressed as a function of  $\Delta H$ ,  $\Delta S$  and  $\Delta C_p$  (using eq. 22 and eq. 23), itself  
 290 depending on the protein chain length denoted  $N$ :

$$\Delta G = \Delta H(N) + \Delta C_p(N)(T - T_h) - T\Delta S(N) - T\Delta C_p(N)\ln(T/T_s) \quad (28)$$

291 with

$$\begin{aligned} \Delta H(N) &= aN + b \\ \Delta S(N) &= cN + d \\ \Delta C_p(N) &= lN + m \end{aligned} \quad (29)$$

292 where  $a, b, c, d, l, m$  are empirical parameters defined for mesophilic and for thermophilic organisms.  
 293 The distribution of chain length over the proteome  $P(N)$  can be known (Zhang, 2000) and is used  
 294 to estimate  $P(\Delta G)$ . It can be modelled by a gamma distribution:

$$P(N) = \frac{N^{\alpha-1} e^{-N/\theta}}{\Gamma(\alpha)\theta^\alpha} \quad (30)$$

295 where  $\theta$  and  $\alpha$  are the parameters of the gamma distribution corresponding to:

$$\begin{aligned} \langle N \rangle &= \alpha\theta \\ \langle (\Delta N)^2 \rangle &= \alpha\theta^2 \end{aligned} \quad (31)$$

296 The brackets represent the mean over all the proteins.  $\Gamma(\alpha)$  is the gamma function evaluated at  
 297  $\alpha$ . The model (eq. 27), presented as universal, has thus only two parameters,  $N_p$  and  $\Delta H^\ddagger$ . It has  
 298 been validated on 12 normalized data sets of prokaryotes.

299 **The heat capacity hypothesis:** Hobbs et al (2013) and Schipper et al (2014) proposed a  
 300 model called the Macromolecular Rate Theory (MMRT) in which the thermal growth curve is  
 301 driven by the heat capacity change of activation  $\Delta C_p^\ddagger$  (*i.e.* the heat capacity difference between  
 302 the ground state and the transition state). More precisely, the growth rate is expressed as:

$$\mu(T) = \frac{k_B}{h} T e^{\Delta G^\ddagger(T)/(RT)} \quad (32)$$

303 where  $k_B$  and  $h$  are the Boltzmann and Planck's constants,  $\Delta G^\ddagger$  is the Gibbs free energy difference  
 304 between the ground state and the transition state of a possible rate-limiting enzyme. Contrary to  
 305 the master reaction model, the MMRT considers that enzymes do not denature easily and are in  
 306 rapid equilibrium with a folded, inactive intermediate (*i.e.* the transition state). The Gibbs free  
 307 energy difference can be here written as:

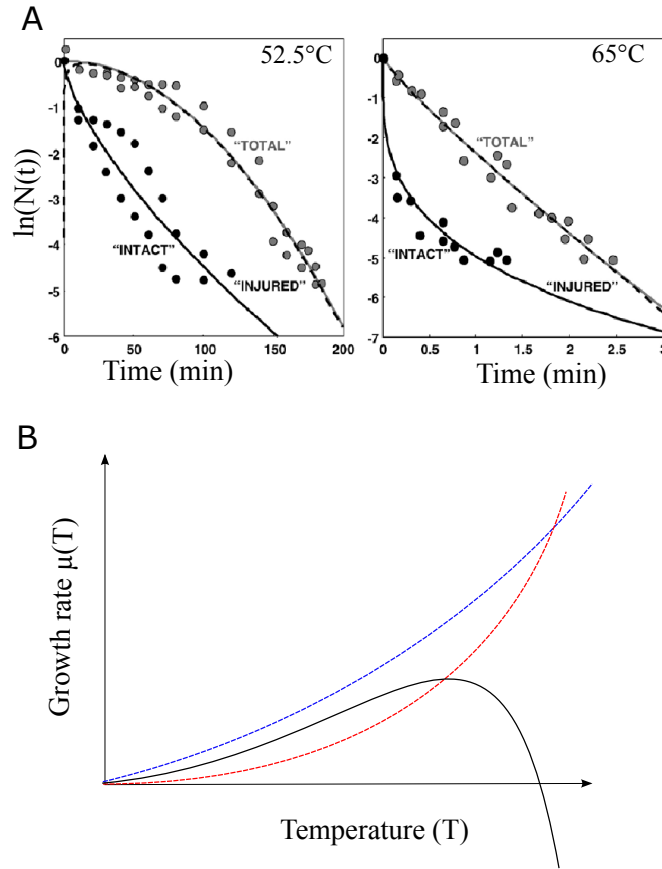
$$\Delta G^\ddagger(T) = \Delta H_{T_0}^\ddagger + \Delta C_p^\ddagger(T - T_0) + T(\Delta S_{T_0}^\ddagger + \Delta C_p^\ddagger \ln(T/T_0)) \quad (33)$$

308 If  $\Delta C_p^\ddagger > 0$ , then the heat capacity difference between the ground state and the transition state  
 309 (*i.e.* the inactive folded enzyme) itself is sufficient to explain the decrease of growth rate above  
 310  $T_{opt}$ . Schipper et al (2014) validated the MMRT model on microbial soil processes data sets.

## 311 2.6 Mortality induced by temperature

312 Warm temperatures increase cell mortality because of protein denaturation and membranes in-  
 313 juries. For phytoplankton, photosystems and electron chain transport are denaturated (Song et al,  
 314 2014), and a transient imbalance between the energy needed and produced must be managed by  
 315 the cell (Ras et al, 2013; Smelt and Brul, 2014; Serra-Maia et al, 2016).

316 So far, models explicitly presenting the mortality rate as a function of temperature are rare.  
 317 The Hinshelwood model explicitly integrates a mortality rate with an Arrhenius law (see fig. 7 B).  
 318 This model turned out to efficiently represent mortality together with growth for the chlorophyta  
 319 *Chlorella vulgaris* (Serra-Maia et al, 2016). Another example is Van Uden (1985) who combined a  
 320 master reaction growth model and an exponential death model for yeast:



**Fig. 7** A, Survival curves at different temperatures for *Listeria innocua* (redrawn from Corradini and Peleg (2006)). B, Hinshelwood model (black curve) with mortality (red curve) as in Serra-Maia et al (2016).

$$\mu(T) = \frac{C e^{-\Delta H^\ddagger/(RT)}}{1 + e^{-\Delta G/(RT)}} - \frac{k_B T}{h} e^{\Delta S_{den}^\ddagger/R - \Delta H_{den}^\ddagger/(RT)} \quad (34)$$

321 where  $\Delta S_{den}^\ddagger$  and  $\Delta H_{den}^\ddagger$  are the entropy and enthalpy of activation of cells mortality.

322 Outside of the thermal niche width, for temperatures above the species  $T_{max}$ , the kinetics of  
 323 cell inactivation is called the survival curve (Moats, 1971) (fig. 7 A); from each survival curve, it is  
 324 possible to infer the mortality rate at a given temperature. Different empirical models have been  
 325 developed, especially in food science, to represent these survival curves (Mafart et al, 2002; Smelt  
 326 et al, 2002; Smelt and Brul, 2014).

### 327 3 Choosing the most appropriate model

328 In this section, we propose a guideline for choosing the most appropriate model depending on the  
 329 study objectives. We summarize and compare the models performance and their applicability to  
 330 phytoplankton in different modeling scenario, and highlight the most appropriate models.

331 The model comparison is based on the analysis of 193 thermal curve responses associated to  
 332 193 different strains, resulting from 130 species (Thomas et al, 2012). This data set includes the  
 333 main phyla of unicellular photosynthetic organisms.

334 An illustration of the model performance for 5 strains of the cyanobacterium genus *Synechococ-*  
 335 *cus* sp. is plotted on fig. S1 (Pittera et al, 2014).

### 3.1 Synthesis of model performance

Three criteria have been considered to assess a model efficiency. The absolute model performance is estimated using  $r^2$ . To account both for the fit quality and the number of parameters, we considered the Akaike Information Criterion (AIC) (Akaike, 1992) and the Bayesian Information Criterion (BIC) (Schwarz et al, 1978) (see table 2 and table S1-S3). The best models are, globally, the empirical models, and the CTMI and the Eppley-Norberg turn out to obtain the best score (see table S2, fig. S2). The Hinshelwood model, in the other way, has the best score among the mechanistic models. It is worth noting here that the CTMI assumes that  $T_{max} - T_{opt} \leq T_{opt} - T_{min}$ , which is not the case for the Eppley-Norberg. Thus, for small data sets with few points near  $T_{opt}$ , the Eppley-Norberg model has a better fit score (see fig. S3).

To highlight the combination of fit quality and other important characteristics, we defined several criterions in table 1. From these criterions, we could derive advantages, limitations and rating for each model (table 1). The CTMI, Bernard&Rémond and the Hinshelwood model obtain the highest score, with the best trade-off between complexity (*e.g.* few parameters), fit quality, calibration easiness and parameters interpretation.

### 3.2 Macroscopic modeling without including mortality

A common scenario when modeling the effect of temperature on phytoplankton is the need of representing the net thermal response, without explicitly representing mortality. The response is generally focusing on growth rate, but it can also represent a detailed physiological processes. Below the optimal temperature, the Arrhenius equation has been widely used, has a good fit, is easy to calibrate and its parameters can be interpreted. However, to represent the whole thermal growth curve, the CTMI is the best choice because its parameters are directly the cardinal temperatures and its calibration is easily possible thanks to a dedicated algorithm. Other similar models (*e.g.* Eppley-Norberg) are also satisfactory. When light is not photoinhibiting, these models can be easily combined with the light effect on growth. In particular, the Bernard&Rémond model is a good trade-off. This latter model has been originally validated on 15 phytoplankton species and here on 193 phytoplankton species (table S1-S3) from the main phytoplankton phyla. The CTMI is thus expected to be the ideal candidate to represent the effect of temperature on phytoplankton communities. The Eppley-Norberg model is also interesting for modeling communities given that from its four parameters, two are considered universal and only two are strain-specific.

### 3.3 Macroscopic modeling with explicit mortality rate

As we pointed out, few studies exist to represent the effect of temperature on phytoplankton mortality. The only model that explicitly represents mortality is the Hinshelwood model. Adapted for phytoplankton (Serra-Maia et al, 2016), this model is thus recommended because its parameters can be interpreted, and the fit quality is acceptable; however, its parameters calibration are not easy on experimental data with few data points. We thus recommend to use the CTMI to generate a patron for the net growth rate. The patron, made of the data points simulated by the CTMI model can then be advantageously used to calibrate the Hinshelwood model.

### 3.4 Physiological or metabolic modeling

The proteome model is certainly the best candidate to explain the thermal growth curve, as it includes the effect of temperature on the whole proteome and has only two parameters. However, it does not fit very well the experimental data for phytoplankton growth rates compared to the empirical models. As for the Hinshelwood model, a patron can be used to artificially increase the number of data points. This model could also be adapted to phytoplankton when light is photoinhibiting.



Model	Advantages	Limitations	Rating
Square-root	Fit quality	No mortality, $T_{opt}$ is not easily defined	***
CTMI	Fit quality, parameters interpretation	No mortality	****
Blanchard	Calibration easiness, fit quality, application to phytoplankton	No mortality $T_{min}$ is not defined	***
<b>Bernard&amp;Rémond</b>	<b>Calibration easiness, fit quality, parameters interpretation, application to phytoplankton</b>	<b>No mortality</b>	<b>*****</b>
Eppley-Norberg	Fit quality, application to phytoplankton	No mortality, implicit link between $T_{opt}$ and $\mu_{opt}$	****
Arrhenius equation	Fit quality below $T_{opt}$	No representation of the decreasing phase above $T_{opt}$	**
Master reaction	Parameters interpretation	$T_{min}$ and $T_{max}$ are undefined	**
<b>Hinshelwood</b>	<b>Fit quality, parameters interpretation, explicit mortality</b>	<b><math>T_{min}</math> is not defined</b>	<b>****</b>
DEB theory	Fit quality	High number of parameters	*
Modified Master reaction	Parameters interpretation	Poorness of fit	**
Proteome based	Parameters interpretation, only 2 parameters	Poorness of fit	***
Heat capacity based	-	Poorness of fit, parameters interpretation not clear	*

**Table 3** Advantages, limitations and rating of the main models for growth rate as a function of temperature. Rating is based on criterion from table 1, from 1 to 5 stars (the latter being better).

## 381 4 Coupling temperature and other environmental factors

### 382 4.1 Factors influencing the thermal growth curve

383 The thermal growth curve is assumed to be obtained in non-limited conditions (Kingsolver, 2009).  
 384 However, some limitations and perturbations usually occur in the environment that may simultane-  
 385 ously involve changes in metabolism. The simplest representation of some multi-factors impact on  
 386 the growth rate is to assume that all the factors are uncoupled. A classical formalism to represent  
 387 the effect of  $n$  uncoupled factors is given by the gamma concept (Zwietering et al, 1993; Augustin  
 388 and Carlier, 2000):

$$\mu = \mu_{opt} \cdot \prod_{k=1}^n \gamma_k \quad (35)$$

389 where  $\mu_{opt}$  is the maximal growth rate when all the  $n$  environmental factors are optimal,  $\gamma_k$   
 390 is a normalized function of the environmental factor  $k$ . One of the  $\gamma_k$  represents the impact of  
 391 temperature.

392 In a more accurate approach, the impact of a factor on the cardinal temperatures can be repre-  
 393 sented (or more generally the parameters of the thermal model can be a function of another factor).  
 394 In this case, these environmental factors are coupled to temperature. For example, temperature  
 395 plays a role on oxygen dissolution in water, and the two factors have then a coupled effect on  
 396 microbial growth rates; this coupling is enhanced for unicellular diazotrophic cyanobacteria which  
 397 are particularly sensitive to the oxygen concentration, because oxygen inhibits their diazotrophic  
 398 activity (Brauer et al, 2013).

399 For the majority of phytoplankton species, the most important physico-chemicals factors are  
 400 light and nutrients (mainly N and P) (Falkowski and Raven, 2013).

### 401 4.2 The interplay between light and temperature in phytoplankton

402 Phytoplankton perform oxygenic photosynthesis to harvest light. Photosynthesis metabolism is  
 403 composed of a dark phase and a light phase, with different thermal sensitivities. The dark phase

404 involves the Rubisco enzyme responsible for CO<sub>2</sub> fixation in the Calvin cycle. In the light phase, at  
 405 low temperatures, the reactions are mainly photochemical and not enzymatic and thus less sensitive  
 406 to temperature. As a consequence, the cell has to balance the energy and electrons transferred from  
 407 photons harvesting and their conversion into chemical energy in the dark phase, depending on the  
 408 temperature (see for example the review by Ras et al (2013)). A shift down to low temperatures  
 409 induces a strong imbalance and thus generates light saturating conditions (see Young et al (2015)).  
 410 However, at high temperatures, the light phase is strongly affected by temperatures as electron  
 411 transport chains and photosystems structural stability is affected (Song et al, 2014) and can induce  
 412 cell mortality.

#### 413 4.2.1 Models assuming an uncoupling between light and temperature effects

414 These models assume that temperature and light are independent factors. For example, the model  
 415 developed by Bernard and Rémond (2012) supposes that the growth rate is expressed as:

$$\mu(T, I) = f(I) \cdot \phi(T) \quad (36)$$

416 where  $\phi(T)$  corresponds to the CTMI (eq. 5) and:

$$f(I) = \mu_{max} \frac{I}{I + \frac{\mu_{max}}{\alpha} \left( \frac{I}{I_{opt}} - 1 \right)^2} \quad (37)$$

417  $\mu_{max}$  is the maximum growth rate at optimal light intensity  $I_{opt}$  and optimal temperature  $T_{opt}$ ,  $\alpha$  is  
 418 the initial slope of the light response curve.  $f(I)$  was built in line with the Peeters and Eilers (1978)  
 419 model with photoinhibition, but reparametrized for a better parameter identification. Bernard and  
 420 Rémond (2012) developed an algorithm to identify the cardinal temperature from data sets with  
 421 different light conditions. This model was validated on 15 phytoplankton species. The hypothesis  
 422 of uncoupling is, however, no longer available at high light intensities (*i.e.* when photoinhibition  
 423 occurs) as temperature is known to play a role in photoinhibition (Jensen and Knutsen, 1993;  
 424 Edwards et al, 2016).

425 The model of Eppley-Norberg modified by Follows et al (2007), uses another formalism to  
 426 represent both temperature and light effect:

$$\mu(T, I) = \mu_{max} \cdot \underbrace{\frac{1}{\tau_1} \left( A^T e^{-B(T-T_0)^c} - \tau_2 \right)}_{\gamma^T} \cdot \underbrace{\frac{1}{\gamma_{max}^I} (1 - e^{-k_p I}) e^{-k_i I}}_{\gamma^I} \quad (38)$$

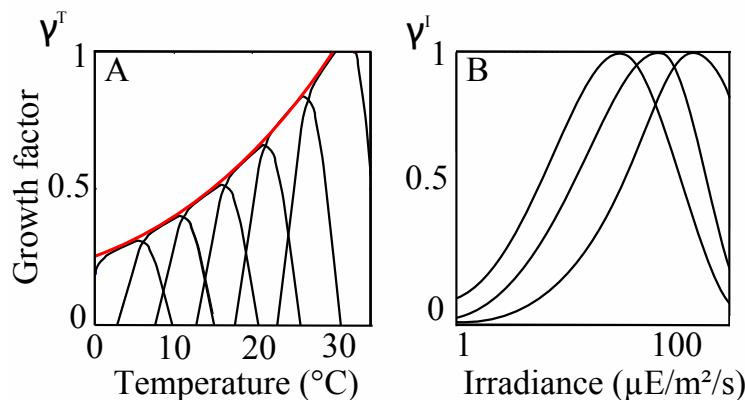
427 where  $\mu_{max}$  is the species maximum growth rate,  $\gamma^T$  and  $\gamma^I$  are respectively the normalized tem-  
 428 perature function and the normalized photosynthesis function. The parameters  $\tau_1$  and  $\tau_2$  ensure  
 429 the normalization of  $\gamma^T$ , while parameters  $A$ ,  $B$ ,  $T_0$  and  $c$  modify its shape by taking into ac-  
 430 count the Eppley hypothesis (see fig.8). Similarly,  $\gamma_{max}^I$  ensures the normalization of  $\gamma^I$ ,  $1 - e^{-k_p I}$   
 431 represents the increase of growth with light at low irradiance and  $k_i$  is a constant associated to  
 432 photo-inhibition.

#### 433 4.2.2 Models considering a coupling between light and temperature

434 The model developed by Dermoun et al (1992) for the unicellular Rhodophyta *Porphyridium cru-*  
 435 *entum* accounts for a complex coupling between light and temperature:

$$\mu(T, I) = 2\mu_m(T)(1 + \beta_1) \frac{I/I_{opt}(T)}{1 + 2\beta_1 I/I_{opt}(T) + (I/I_{opt}(T))^2} \quad (39)$$

436 where  $\mu_m(T)$  is the maximum specific growth rate at a given temperature  $T$ ,  $I_{opt}$  is the optimal  
 437 irradiance at a given temperature  $T$  and  $\beta_1$  is the shape factor for limiting irradiance.  $\mu_m(T)$   
 438 and  $I_{opt}(T)$  are rational functions (see Dermoun et al (1992)). It is worth noting that the tight  
 439 coupling between light and temperature in this model leads to identifiability problems partially due  
 440 to large number of parameters (9 parameters in the model). Furthermore, when light is limiting,  
 441 the coupling between light and temperature becomes loose.



**Fig. 8** A, Eppley curve normalized at 30°C. B, photosynthesis as represented in eq. 38. The figure is redrawn after Follows et al (2007).

#### 442 4.3 The interplay between nutrients and temperature

443 Phytoplankton growth in the oceans is often limited by nitrogen (N) or phosphorus (P). When  
 444 limiting, these nutrients strongly impact the thermal growth curve (Pomeroy and Wiebe, 2001;  
 445 Thomas, 2013; Thomas and Litchman, 2016). Trace nutrients such as trace metals or essential  
 446 vitamins can also play an important role on growth but their interplay with temperature is largely  
 447 unknown.

448 Thomas (2013) has developed a model taking into account the nutrient effect (N), assuming  
 449 that anabolism is temperature-dependent and nutrient-dependent, whereas catabolism or mortality  
 450 only depend on temperature:

$$\mu(T, N) = b_1 e^{b_2 T} \frac{N}{N + K} - (d_1 e^{d_2 T} + d_0) \quad (40)$$

451 where  $b_1$ ,  $b_2$ ,  $d_1$ ,  $d_2$  are Arrhenius parameters for anabolism and catabolism, respectively, and  $K$   
 452 is the half-saturation constant of a Michaelis-Menten kinetics of nutrient uptake.  $d_0$  is a constant  
 453 catabolism rate independent of temperature. Nutrient limitation leads to a decrease of the thermal  
 454 niche width,  $T_{opt}$  and  $\mu_{opt}$  (see fig. 9 A). The model has been validated on temperature and nutrient  
 455 experiments conducted with the phytoplankton diatom species *Thalassiosira pseudonana* (Thomas  
 456 et al, 2017).

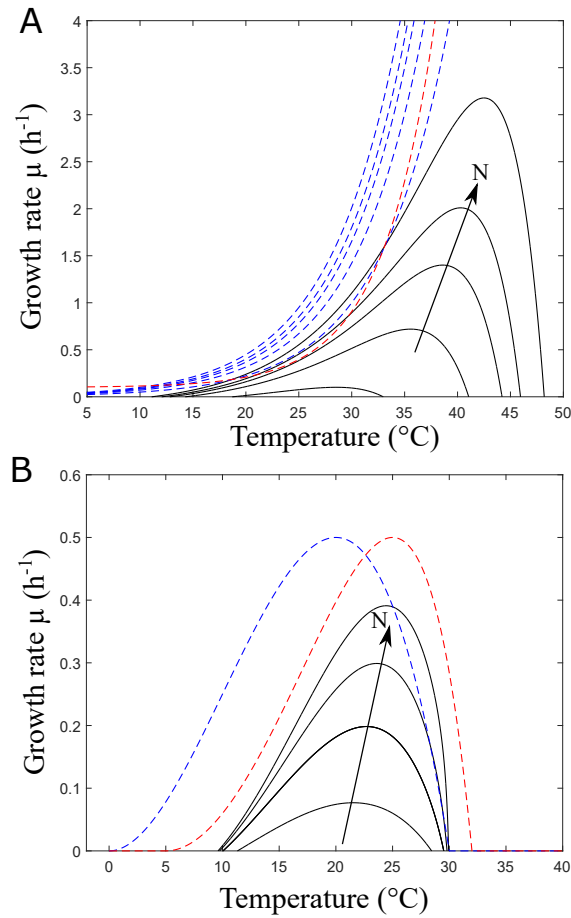
457 Grimaud (2016) has developed a dynamical model taking into account temperature and nutrient  
 458 for eukaryotes phytoplankton species, based on the Droop model (Droop, 1968). In balanced-growth  
 459 conditions, the model gives the following thermal growth curve:

$$\mu(T, N) = \frac{\phi_2(T)\phi_1(T)\rho(N)}{\phi_1(T)\rho(N) + \phi_2(T)Q_0} - m \quad (41)$$

460 where  $\phi_1(T)$  and  $\phi_2(T)$  are CTMI equations for nutrients and carbon uptake,  $\rho(N)$  is a normalized  
 461 Michaelis-Menten equation,  $Q_0$  corresponds to the minimal internal nutrient quota needed to grow,  
 462  $m$  is the constant mortality/catabolism rate. Fig. 9 B shows that a nutrient limitation leads to  
 463 a decrease of  $T_{opt}$  and  $\mu_{opt}$ , in line with Thomas (2013). However, the amplitude of the thermal  
 464 niche width is less marked, and is only reduced for strong nutrient limitation (see fig. 9 B). Also,  
 465 these results depend on the difference between  $\phi_1(T)$  and  $\phi_2(T)$ .

#### 466 5 Accounting for temperature variations

467 In the natural environment, cells experience temperature fluctuations at different time-scales, rang-  
 468 ing from days to seasons, influencing their physiology and forcing them to acclimate (Ras et al,  
 469 2013; van Gestel et al, 2013). The question is then how to deal with these variations, while thermal  
 470 growth curves are obtained in balanced conditions.



**Fig. 9** Growth rate as a function of nutrient and temperature  $\mu(T, N)$ . The black lines correspond to different nutrient values, increasing with the arrow. A, model of Thomas (2013). The blue and red dashed lines correspond to the positive and negative terms of eq. 40, respectively. B, model of Grimaud (2016). Blue and red dashed lines correspond to  $\phi_1(T)$  and  $\phi_2(T)$  of eq. 41, respectively.

#### 471 5.1 Assuming instantaneous acclimation at large time scale

472 The specific growth rate  $\mu(T)$  described in section 2.1 for balanced growth has been used as such  
 473 when temperature is time-varying, assuming that the effect of temperature is instantaneous (see  
 474 for example Baranyi and Roberts (1995); Baranyi et al (1995)). This approximation is valid in  
 475 particular for slow variations of temperature, such as annual fluctuation of sea temperature.

#### 476 5.2 Acclimation to temperature variations

477 Cell acclimate to temperature by adjusting the biosynthesis of key components (Hall et al, 2010;  
 478 Ras et al, 2013). For example, Geider (1987) showed that phytoplankton cells are able to adapt  
 479 their pigment content when temperature changes. The chlorophyll concentration is adjusted to  
 480 the photon flux and to the cells capacity of converting it into chemical energy. The carbon to  
 481 chlorophyll ratio ( $\theta = Chl_a : C$ ) increases with temperature, and, following Geider (1987), this  
 482 ratio converges after an acclimation phase to  $\theta^*(T)$ :

$$\theta^*(T) = \frac{e^{kT}}{(a - bT)e^{kT} + cI} \quad (42)$$

483 where  $a$ ,  $b$ ,  $c$ ,  $k$  are constants and  $I$  is the light intensity. However, eq. 42 is valid for balanced  
 484 growth.

485 Dynamical models representing acclimation should therefore consider the different cellular com-  
 486 ponents, and include the temperature effect on each reaction kinetic. Models for phytoplankton  
 487 including chlorophyll have been proposed for example by Geider et al (1998), but the temperature  
 488 effect has been overlooked (assuming that all the kinetics have the same temperature dependence).

489 In Bernard et al (2015), an equation for cell acclimation is proposed, which can be straightfor-  
 490 wardly extended to acclimation to temperature:

$$\dot{\theta} = \delta \mu(T) [\theta^*(T) - \theta] \quad (43)$$

491 where  $\delta$  is a parameter modulating the acclimation rate, which is assumed proportional to the  
 492 growth rate  $\mu$ . This kind of models is of particular interest given that it can deal with both  
 493 temperature fluctuations and the interplay with other factors such as light, but more experimental  
 494 data are required for calibration and validation.

## 495 6 Conclusion and future developments

496 To better picture the temperature effect, there is an urgent need for standard protocols, as proposed  
 497 by Boyd et al (2013), fulfilling two crucial points: *i*/ assess the growth rate with biomass proxies  
 498 which are not influenced by temperature; *ii*/ consider acclimation periods of at least one week for  
 499 each temperature. Such a protocol is required to isolate the impact of temperature on growth and  
 500 to compare different experimental results.

501 Despite their simplicity, empirical models turn out to be very acute for representing the exper-  
 502 imental data sets for phytoplankton (see fig. 2). Nonetheless, to be efficient, these models must be  
 503 associated to tailored calibration algorithms in line with Bernard and Rémond (2012) to rapidly  
 504 fit a data set and quantify the uncertainty.

505 The mechanistic approach brings a complementary viewpoint in the modeling of the thermal  
 506 growth curve but also in representing the temperature response for non-balanced growth conditions.  
 507 Temperature plays a concurrent role on enzyme activity and therefore on reactions kinetics, and  
 508 on cell structural stability. Most of the mechanistic models consider that a single enzyme controls  
 509 growth at low temperatures (*e.g.* MMRM and proteome-scale approach) whereas temperature  
 510 affects enzyme and protein conformational stability and leads to a decrease of growth at high  
 511 temperatures (Ghosh et al, 2016). Despite the recent development of a promising unicellular growth  
 512 model (Corkrey et al, 2014), this ‘proteome paradigm’ should be further investigated for several  
 513 reasons. First, the effect of temperature on protein stability is still relatively unclear given that we  
 514 do not know, for example, in which extent proteins denaturation proceeds the same way in vivo as in  
 515 vitro (Leuenberger et al, 2017). Second, other structural components play an important role in the  
 516 cell thermal stability, and especially on membrane fluidity (Caspeta et al, 2014). Third, cells have  
 517 the capacity to repair their damages and regrow after a heat shock (Li and Srivastava, 2004) which is  
 518 not clearly understood, as well as the molecular mechanisms protecting against mortality (Ghosh  
 519 et al, 2016). Finally, the link between the mortality rate and protein denaturation still remains  
 520 unclear; it is for example not known how mortality increases between  $T_{opt}$  and  $T_{max}$ . Mortality  
 521 models in line with Serra-Maia et al (2016) are needed. In addition to the ‘proteome paradigm’  
 522 limits, the effect of temperature on cells kinetics is not limited to one enzyme controlling growth, but  
 523 apply for all reactions. Some authors, for example, claim that the thermal growth curve is the result  
 524 of an imbalance of cellular energy allocation (called the metabolic hypothesis) (Ruoff et al, 2007;  
 525 Poertner, 2012; Zakhartsev et al, 2015). The use of metabolic models under non-balanced growth  
 526 should be used to challenge this problematic (Baroukh, 2014). Additionally, models describing the  
 527 dynamics of acclimation should be used to tackle the cellular response to temperature variations  
 528 at different time-scales (Ras et al, 2013).

529 This work is a step towards the comprehension of the effect of global warming on phytoplankton.  
 530 To do so, new thermal models should be designed to represent the temperature coupling with  
 531 the most important growth factors. For phytoplankton, some models accounting for light and  
 532 temperature have been validated on experimental data (Bernard and Rémond, 2012), but we do  
 533 not know in which extent they can be used. For example, the effect of temperature at high light  
 534 intensity has not clearly been investigated. The development of cell-scaled models representing  
 535 the different states of the photosystem centers and their temperature sensitivities (as done, for  
 536 example, by Duarte (1995)) should help to better understand the temperature and light coupling.

537 For nutrients, the coupling effect of temperature and starvation have a drastic impact on growth,  
538 and models are in development (Thomas, 2013; Thomas et al, 2017).

539 It is worth noting that we did not describe adaptation models at the evolutionary time-scale  
540 which are needed to understand long time effects of an increase in temperature on the thermal  
541 response. These models, mostly based on the adaptive dynamics theory, are currently being de-  
542 veloped (Thomas, 2013; Grimaud, 2016) and should be the next stage to understand the effect of  
543 global warming on oceans.

**Acknowledgements** This work was supported by the ANR Purple Sun project ANR-13-BIME-004. We are grateful to Quentin Béchet, Colin Kremer, Mridul Thomas and the Litchman&Klausmeier lab for their interesting comments on the paper.

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