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THERMODYNAMIC APPROACH TO MODELING BIOFUELS PRODUCTION FROM MICROALGAE AND CYANOBACTERIA: THE ROLE OF ELECTROCHEMICAL POTENTIAL

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(communicated by Paolo V. Giaquinta)

ABSTRACT. Biofuels from 3rd-generation feed-stocks like microalgae and cyanobacteria are considered possible replacements of fossil fuels and a means to reduce emissions of the greenhouse gas CO₂. There is a need to understand how to control microbial growth by manipulating environmental conditions to increase photosynthetic biofuel productivity and/or reduce manufacturing costs. A novel, non-equilibrium, bio-thermodynamic-based model was developed here to fundamentally link electrochemical potential, membrane electric potential, trans-membrane pH gradient, and external temperature with microbial proliferation and bio-system behaviour.

1. Introduction

Most of society uses fossil fuels as its main source of energy with two related consequences (Rittmann 2008): (i) the risk of geopolitical turmoil and (ii) environmental pollution and climate change. Entropy generation thermodynamically influences many Earth system processes (Sertorio 1990; Volk and Pauluis 2010; Kleidon 2012; Westra *et al.* 2014; Grisolia *et al.* 2020), with particular regards to the thermal fluxes in the atmosphere (Sertorio 1990; Kleidon 2009, 2010a,b; Volk and Pauluis 2010; Westra *et al.* 2014; Lucia *et al.* 2021). Consequently, analysis of global thermometric measurements since 1850 indicate that recent decades have been the hottest in human history (Trifirò 2019) and that global temperatures are predicted to continually increase by 2-4°C before the end of this century due to likely anthropogenic contributions and emissions of greenhouse gases.

At a 2017 UN IPCC Conference in Marrakesh, Morocco, it was suggested that limiting a 2°C temperature increase was necessary to prevent exceeding a thermal threshold for possible disastrous climate change (Trifirò 2019). Pollution also lowers quality of life due to its human-health and environmental consequences (Barman *et al.* 2010; Cohen *et al.* 2017; Contiero *et al.* 2019). Humans must adopt more sustainable practices to limit the deleterious effects of pollution and climate change. Fundamental improvements are required in technologies for power generation and transportation, industrial production, and

agriculture. These may include a more widespread manufacture and adoption of alternative and sustainable biofuels which offer (Chum and Overend 2001; Nigam and Singh 2011; Catalán-Martínez *et al.* 2018) three main advantages over fossil fuels (Lang *et al.* 2001; Lee and Lavoie 2013):

- availability: biofuels can be obtained from different types of biomasses;
- technical and environmental feasibility: biofuels can be obtained from biomasses of living organisms that photosynthetically consume, the same amount of CO₂ emitted by the combustion of the same biofuels;
- economic competitiveness: countries can cultivate locally the raw biomass material for biofuels production.

There are three different, classifying generations of biofuels (Gambelli *et al.* 2017; Lucia and Grisolia 2018):

- the 1st generation (Immethun *et al.* 2016) are obtained from food crop yields and compete directly with food;
- the 2nd generation (Bensaid *et al.* 2012; Battista *et al.* 2016; Saladini *et al.* 2016) are obtained by non-edible biomasses like energy terrestrial crops, such as *Jatropha*, or wastes from the agricultural, municipal or food sectors, and compete with non-arable land;
- the 3rd generation (Alaswad *et al.* 2015) are obtained from photosynthetic microorganisms like microalgae and cyanobacteria that can grow on non-arable land and in saltwater or brackish waters with no need for pesticides, fungicides or herbicides. These do not compete with resources of the 1st or 2nd generation feedstocks and are considered more sustainable with respect to maintenance of biodiversity (Chowdhury and Loganathan 2019; Correa *et al.* 2019), ethical responsibility, energy and costs requirements (Chisti 2007; Rodolfi *et al.* 2009; Mata *et al.* 2010; Carriquiry *et al.* 2011; Pols and Spahn 2014; Ziolkowska and Simon 2014; Leong *et al.* 2019). However, 3rd-generation biofuels aren't yet as competitive as fossil fuels because of their high costs of production and extraction in relation to the amount of fuel obtainable per unit volume of culture (Enamala *et al.* 2018).

In this context, microbial, phototrophic biofuel production can be modeled, simulated, analysed and optimized (Su *et al.* 2015; Saravanan *et al.* 2018; Musa *et al.* 2019), via a thermodynamic approach to related biophysical processes. Microalgal and cyanobacterial outer membranes, comprised typically of phospholipids and proteins, are crucial for life. Such microorganisms continuously interact with and modify their environment through such membranes via secretion of enzymes, toxins or pheromones, and macromolecules on their outer membrane surfaces. Outer membranes represent a partial barrier to the diffusion and/or active transport of water-soluble compounds and isolate the cytoplasm from external environment (Maloney 2002). Membranes modulate inflow of nutrients and outflow of waste products with a related restoration of ionic gradients changed by the transport systems. Cells maintain their ionic concentration at a pH of ~ 7.5 , usually 10 mmol L⁻¹ for Na⁺, 200 mmol L⁻¹ for K⁺, and 0.1 mmol L⁻¹ for Ca²⁺, etc., by using external sources of energy like adenosine triphosphate (ATP) hydrolysis generated by electrochemical ion gradients (Maloney 2002). Indeed, microbial electrical signalling was experimentally proven to regulate a great variety of physiological processes like cellular proliferation (Stratford *et al.*

2019), which is mediated by membrane electric potential (McCaig *et al.* 2005; Levin 2014; Prindle *et al.* 2015; Sirec *et al.* 2019).

Many previous theoretical modeling and computational studies of cellular membrane mechanics did not fully describe membrane dynamical and chemical behaviour (Arroyo *et al.* 2018). We recently developed a thermodynamic approach to mutualism (Lucia and Grisolia 2020b,d), to improve sustainable biodiesel production from eukaryotic fungi and microalgae (Shurin *et al.* 2013; Kazamia *et al.* 2014; Santos and Reis 2014; Cho *et al.* 2015; Cooper and Smith 2015; Heimann 2016; Ramanan *et al.* 2016; Lucia and Grisolia 2020a). This included prediction of cyanobacterial and microalgal behaviour via a new non-equilibrium thermodynamic model simulating outer periplasmic membranes and/or (peptidoglycan, chitin, cellulosic, etc.) cell walls. Little is still understood about cellular mechanisms to decode external, electrical signal information (Stratford *et al.* 2019).

We wish to further determine how known conditions of microorganisms environments can be used to control and improve biofuel production. For this, we use a non-equilibrium thermodynamic approach to predicting cellular membrane heat and mass transport, recently developed and applied for microbial growth (Lucia and Grisolia 2020a), and disease progression like that for cancer (Lucia 2015; Lucia and Grisolia 2020b,c,e) and glaucoma (Lucia and Grisolia 2020d). Predicted results were in agreement with and validated by experimental results in literature, both in relation to cancer (Ambrose *et al.* 1956; Tokuoka and Marioka 1957; Balitsky and Shuba 1964; Jamakosmanovic and Loewenstein 1968; Cone 1969, 1970, 1971; Altman and Katz 1976; Foyouzi-Youssefi *et al.* 2000; Pinton *et al.* 2000, 2001; Berridge *et al.* 2003; Rizzuto *et al.* 2009a; Sundelacruz *et al.* 2009; Lobikin *et al.* 2012; Marchi *et al.* 2012; Schwab *et al.* 2012; Akl and Bultynck 2013; Bononi *et al.* 2013; Yang and Brackenbury 2013; Akl *et al.* 2014; Rimessi *et al.* 2014; Giorgi *et al.* 2015a,b,c; Stewart *et al.* 2015; Giorgi *et al.* 2019) and to glaucoma (Gupta and Yucel 2007; Wax *et al.* 2008; Yucel and Gupta 2008; Bejan 2009; Imamura *et al.* 2009; Tezel 2013; Soto and Howell 2014; Shum *et al.* 2016; Parsadaniantz *et al.* 2020). Therefore, we further develop and validate here a model that builds upon and extends a simplified model of microbial life cycle based on a thermodynamic Peltier-Seebeck transition in membrane ion fluxes (Lucia and Grisolia 2020a) applied in different bio-systems analyses (Lucia and Grisolia 2020b,d) to predict the influence of outer membrane potential in microbial behaviour and biofuel production. By the Peltier-Seebeck analogy, microbial life cycles are represented by two thermodynamic processes:

- continuous microbial energy generation (metabolism), due to ion fluxes: ionic and metabolic fluxes are described by imposing a null heat flux;
- continuous heat fluxes from microbial cells to their environment: the outwards heat transfer from cell to its environment is described by imposing null ion fluxes.

This allows the analysis of the thermodynamic behaviour of the microbial bio-system.

2. Materials and methods

Microalgae and cyanobacteria can be depicted and modeled as simple black-box thermodynamic engines which exchange energy (*i.e.*, heat and work) and mass (*i.e.*, charged ions and uncharged compounds) with their environment via their outer membranes which serve as physical boundaries of open systems. Polychromatic light, from the Sun or artificial

sources, like LEDs and fluorescent bulbs, are the external heat and light intensity source for photosynthesis, while external molecular oxygen and organic carbon like glucose are the energy source for aerobic respiration. Cellular outer membranes are a double lipid layer that separates internally-bound cytoplasm from the cell's external environment. Thermophysical properties of the outer membranes (*i.e.*, conductivity, convective and radiative heat transfer coefficients, effective diffusivity, tortuosity, thickness, porosity, density, surface area, cellular volume, etc.) relate to heat and mass transfer. Optical properties, like scattering and absorption coefficients, are influenced by the outer membrane as well as the network of internal folded membranes housing organelles (*i.e.*, mitochondria, chloroplasts, Golgi apparatus) or lipid bodies containing neutral triacylglycerides that serve as pre-cursors to biofuels. Such optical properties in turn influence the gradient in solar or artificial light intensity and wavelength inside the microalgal or cyanobacterial cell. Outer membrane proteins may serve as channels for the inflows and outflows of mass and ions. These trans-outer membrane fluxes influence internal and external ion concentrations and related pH and trans-internal membrane electric potential variations.

Cyanobacterial and microalgal metabolic and biochemical processes, like cellular aerobic respiration and photosynthesis, are internal thermodynamic transformations needed for cellular maintenance, nutrient uptake, heat dissipation, growth, division, and proliferation. For instance, ATP synthases in microalgae are complex, multi-subunit enzymes which convert electrochemical H^+ ion gradient potentials into mechanical work to spin and phosphorylate ADP to ATP. These electrochemical gradients occur across either internal mitochondrial membranes or internal chloroplast thylakoidal membranes and are, respectively, created via electron transport chain with O_2 as final electron acceptor of oxidative phosphorylation or created via proton motif force with $NADP^+$ as final electron acceptor for non-cyclic or cyclic photophosphorylation. The discharged heat and outflow of matter (ions) are the focus of the thermodynamic analysis for this study.

A non-equilibrium thermodynamic approach to simulate cellular membrane phenomena is obtained by first introducing the Onsager general phenomenological relations, previously related only to membrane electric potential, and, here generalised by introducing the electrochemical potential (Callen 1960; Yourgrau *et al.* 1982; Goupil 2011; Goupil *et al.* 2011; Lucia and Grisolia 2020a,b):

$$\begin{cases} \mathbf{J}_e = -L_{11} \frac{\nabla \mu_e}{T} - L_{12} \frac{\nabla T}{T^2} \\ \mathbf{J}_Q = -L_{21} \frac{\nabla \mu_e}{T} - L_{22} \frac{\nabla T}{T^2} \end{cases} \quad (1)$$

where \mathbf{J}_e [$A\ m^{-2}$] is the net current density, if the effect of multiple different species of ions are considered, or the effect of one species if only one ion species is considered, \mathbf{J}_Q [$W\ m^{-2}$] is the heat flux, $\mu_e = \mu + ze\phi$ [$J\ mol^{-1}$] is the electrochemical potential, with μ [$J\ mol^{-1}$] the chemical potential, ze [$A\ s\ mol^{-1}$] is the electric charge, and ϕ [V] the membrane potential, T is the living cell's outer environmental temperature [K] and L_{ij} represent the adimensional phenomenological coefficients, such that (Katchalsky and Currant 1965) $L_{12}(\mathbf{B}) = L_{21}(-\mathbf{B})$ (Onsager-Casimir relation: de Groot and Mazur 1962), $L_{11} \geq 0$ and $L_{22} \geq 0$, and $L_{11}L_{22} - L_{12}L_{21} > 0$ (Katchalsky and Currant 1965). These results can be

used to model the cellular life cycle of microorganisms by further introducing two related processes (Lucia and Grisolia 2020a,b):

- a continuous energy generation (metabolism), due to the ion fluxes: ionic and metabolites fluxes are described by imposing $\mathbf{J}_e \neq \mathbf{0}$ and $\mathbf{J}_Q = \mathbf{0}$;
- a continuous heat fluxes from microbial cell to its environment: heat transfer from the cell to its external environment can be described by imposing $\mathbf{J}_e = \mathbf{0}$ and $\mathbf{J}_Q \neq \mathbf{0}$.

In this way, we can divide the cellular life cycle into two thermodynamic processes, as commonly done in thermodynamics for complex processes (Callen 1960; Lucia and Grazzini 1997). If the ions and metabolites fluxes occur, $\mathbf{J}_e \neq \mathbf{0}$ and $\mathbf{J}_Q = \mathbf{0}$. Therefore, Eqs. (1) are used to obtain (Callen 1960; Yourgrau *et al.* 1982; Lucia and Grisolia 2020a) the following relation:

$$\frac{d\mu_e}{dT} = -\frac{L_{21}}{L_{11}} \frac{1}{T} \quad (2)$$

with a related heat flux (Callen 1960; Yourgrau *et al.* 1982):

$$\frac{du}{dt} = -\nabla \cdot \mathbf{J}_Q \quad (3)$$

where u [J m^{-3}] is the internal energy density. Considering the living microorganisms in a fluid, conductive heat transfer can be neglected because it is very small compared to convective and radiative heat transfer. Consequently, living phototrophs like microalgae and cyanobacteria exchange heat with their environment primarily by convective transmission and thermal infrared emission. Based on the First Law of Thermodynamics, it follows (Lucia and Grisolia 2020c,e):

$$\frac{du}{dt} dV = \delta\dot{Q} = -\alpha(T - T_0) dA - \varepsilon_{irr} \sigma_{SB} (T^4 - T_0^4) dA \quad (4)$$

where $\varepsilon_{irr} \approx 0.97$ is the emissivity factor (López *et al.* 2012; Lam *et al.* 2014; Couradeau *et al.* 2016), $\sigma_{SB} = 5.67 \times 10^{-8} \text{ W m}^{-2}\text{K}^{-4}$ is the Stefan-Boltzmann constant, $\alpha \approx 0.023 Re^{0.8} Pr^{0.35} \lambda / \langle R \rangle$ is the coefficient of convection, A [m^2] is the area of the external surface of the cell membrane, V [m^3] is the cell volume, T [K] is the mean temperature of the external surface of the microorganisms membrane, and T_0 [K] is the temperature of their external environment. Equations (3) and (4), together with the Divergence Theorem (Apostol 1969), can be combined to yield the heat flux results:

$$J_Q = \alpha(T - T_0) + \varepsilon_{irr} \sigma_{SB} (T^4 - T_0^4) \quad (5)$$

from which it follows:

$$\dot{Q} = \int_A \mathbf{J}_Q \cdot \hat{\mathbf{n}} dA \approx \alpha(T - T_0)A + \varepsilon_{irr} \sigma_{SB} (T^4 - T_0^4)A \quad (6)$$

Equation (1) and the second hypothesis of our approach ($\mathbf{J}_e = \mathbf{0}$, $\mathbf{J}_Q \neq \mathbf{0}$) are used to obtain the following (Lucia and Grisolia 2020a):

$$\frac{d\mu_e}{d\ell} = \frac{T J_Q}{\left(L_{22} \frac{L_{11}}{L_{12}} - L_{21}\right)} = - \frac{\alpha T (T - T_0) + \varepsilon_{irr} \sigma_{SB} T (T^4 - T_0^4)}{\left(L_{22} \frac{L_{11}}{L_{12}} - L_{21}\right)} \quad (7)$$

where ℓ is the length of microbial outer membrane [m] and $|\nabla\mu_e| \approx d\mu_e/d\ell$. Equation (7) represents a link between the microbial outer membrane electrochemical potential and external temperature with heat exchange. Now, Eqs. (5) and (7) allow us to obtain:

$$J_Q = \alpha (T - T_0) + \varepsilon_{irr} \sigma_{SB} (T^4 - T_0^4) \approx - \frac{1}{T} \left(L_{22} \frac{L_{11}}{L_{12}} - L_{21}\right) \frac{\partial\mu_e}{\partial\ell} \quad (8)$$

Considering that $\varepsilon_{irr} \sigma_{SB} (T^4 - T_0^4) \ll \alpha (T - T_0)$, Eq. (8) can be simplified as:

$$\alpha T (T - T_0) = - \left(L_{22} \frac{L_{11}}{L_{12}} - L_{21}\right) \frac{\partial\mu_e}{\partial\ell} \quad (9)$$

Considering that (Goupil *et al.* 2011):

$$\left(L_{22} - L_{21} \frac{L_{12}}{L_{11}}\right) = K_J T^2 \quad (10)$$

where K_J is the Thomson coefficient (Goupil *et al.* 2011), the following is obtained:

$$\frac{\partial\mu_e}{\partial\ell} = \frac{\partial\mu_e}{\partial T} \frac{\alpha}{K_J} (T_{surf} - T_0) \quad (11)$$

which, considering that $\mu_e = \mu + ze\phi$, is used to obtain the following:

$$\frac{\partial\mu}{\partial\ell} = -ze \frac{d\phi}{d\ell} + \frac{\partial\mu_e}{\partial T} \frac{\alpha}{K_J} (T_{surf} - T_0) \quad (12)$$

The chemical potential is defined as (Callen 1960):

$$\mu_i = \left(\frac{\partial G}{\partial n_i}\right)_{T,p,n_{k \neq i}} \approx \frac{G}{n_i} = g \quad (13)$$

where G [J] is the Gibbs energy, g [J mol⁻¹] is the Gibbs molar specific energy, n is the number of moles, and p [Pa] is the pressure. Gibbs Free energy is related to the membrane electric potential by the Nernst equation (Grabe *et al.* 2000):

$$\Delta g = F \Delta\phi - 2.3RT_0 \Delta\text{pH} \quad (14)$$

where $F = 96485$ A s mol⁻¹ is the Faraday constant and $R = 8.314$ J mol⁻¹ K⁻¹ is the universal constant of ideal gas. Incorporation of Eq. (14) into Eq. (12) yields the following:

$$\frac{\partial \mu_e}{\partial T} = \frac{K_J}{\alpha} \frac{F + ze}{T_{surf} - T_0} \frac{d\phi}{d\ell} - \frac{K_J}{\alpha} \frac{2.3RT_0}{T_{surf} - T_0} \frac{dpH}{d\ell} \quad (15)$$

Furthermore, the characteristic length in Eq. (12) is defined as $\langle R \rangle = V/A$ [m]. For this work, the membrane refers to the entire outer cellular envelope. For instance, the cyanobacteria envelope usually consists of an outer gelatinous membrane, a peptidoglycan cell wall and an inner plasma membrane.

3. Results

The novel derived Eq. (12) represents a fundamental link between the chemical potential gradient and the electric potential gradient across the outer membrane of a photosynthetic microorganism, the thermo-physical properties of the outer membrane, and the external environmental conditions like fluid temperature, weighted by the Carnot coefficient. The electro-chemical potential variation with temperature in Eq. (15) depends on the trans-membrane pH gradient. This is in accordance with the previously analysed behaviour of lipid membranes and their relationship with external chemical stimuli. Indeed, lipid membranes are extremely responsive to chemical stimuli, particularly to pH gradients (Arroyo *et al.* 2018), as experimentally proven for synthetic membranes (Sorre *et al.* 2009; Arroyo *et al.* 2018).

The second fundamental quantity in Eq. (12) is the characteristic length $\langle R \rangle = V/A$. This is a geometrical property related to the shape or morphology of microorganisms. Its role is important in heat, mass, momentum, and light transfer. Recently, cell mechano-adaptation was related to the interplay between membrane tension and curvature generation (Morris and Homann 2001; Shi and Baumgart 2015), further suggesting a fundamental role of characteristic length in the biological behaviour of microorganisms.

The third fundamental quantity of Eq. (12) governing microbial behaviour of the microorganisms is controllable, external environmental temperature. In general, as environmental temperature increases and approaches the intracellular temperature of microorganisms, the cellular outer membrane potential increasingly depolarizes. When environmental temperature exceeds the microorganism's intracellular temperature, hyperpolarisation occurs.

4. Discussion and conclusions

Microbial electrical signalling is an overlooked topic of research. Greater interest in the analysis of the cellular membrane dynamics of membrane is emerging. Research on intra- and inter-cellular signalling has pointed out its role in the regulation of fundamental physiological processes (Stratford *et al.* 2019; Benarroch and Asally 2020). A greater understanding of the effects of the exogenous stimuli and electrophysiology on microalgae and cyanobacteria can be used to enhance biofuel and bioplastics production *via* synthetic biology or other tools (Schloss *et al.* 2016). In particular, up to now, the outer membrane potential of microalgae and cyanobacteria hasn't been thoroughly explored or modeled.

Biofuel and bioplastic production is related to cellular growth rate and proliferation, which are in turn controlled by a multitude of factors, including by membrane electric

potential and resulting ATP synthesis (Ramos *et al.* 1976; Kaim and Dimroth 1999; Kotnik and Miklavčič 2000; Strahl and Hamoen 2010).

Our model is supported and experimentally validated by various sources (Harold 1977; Krab and van Wezel 1992; Angelova *et al.* 2018). In particular, exogenous electrical stimulus was proven to shape the proliferative capacity of microorganisms, by inducing hyper-polarisation in the cells (Stratford *et al.* 2019). Experimental estimation of the energy requirement required by the bacterium *Escherichia coli* to maintain its membrane electric potential is around the half of its total energy consumption (Milo and Phillips 2015). This result highlights the fundamental role of the membrane electric potential in microbial life. Furthermore, the correlation between external factors (*i.e.*, temperature and sources of inorganic carbon) and microalgal growth is well-documented. For instance, biomass dry weights and/or cell densities are evidently higher at 37°C (ethanol and acetate result, respectively, $3.43 \pm 0.08 \text{ g L}^{-1}$ and $0.93 \pm 0.12 \text{ g L}^{-1}$, for *Clostridium carboxidivorans* (Shen *et al.* 2020)) compared to at 25°C (ethanol and acetate result, respectively, $1.58 \pm 0.03 \text{ g L}^{-1}$ and $0.61 \pm 0.15 \text{ g L}^{-1}$, for *Clostridium carboxidivorans* (Shen *et al.* 2020)).

Higher microbial growth temperatures generally shortens the lag period and stimulates nutrient uptake, metabolism, and cellular division (Price and Sowers 2004). In our mathematically derived model, cellular metabolism is accounted for by the surface temperature, while conditioning is accounted for by the environmental temperature. Particularly for photosynthetic algae and cyanobacteria as 3rd-generation feed-stocks to sustainable biofuels, additive and multiplicative Monod's growth law (Monod 1950) relates microbial growth rate as a function of the limiting nutrient concentration and light intensity (Saadat *et al.* 2020a). During the second half of the 20th century, many experiments were conducted to measure heat production during microbial growth to evaluate the entropy variation in growing cells and their environment. Consequently, some thermodynamic approaches to microbial growth were developed to further our comprehension of what principally influences microbial growth processes. However, such approaches were limited by their consideration of microbial metabolism as a black box. Recently, new theories were developed to model metabolism and better explain microbial growth. However, these did not consider fundamentally-important thermodynamic limitations, and a closer interaction between these fields is thus required. For instance, growth and decaying rates of dissipated heat, and the maximal rate of self-replication increase with heat dissipation (England 2013; Saadat *et al.* 2020a). Furthermore, replication rates increase with higher internal entropy. Both these properties are not commonly quantified in microbial organisms. An enormously valuable and synergistic insight from previous approaches can be obtained to extend our understanding of thermodynamic limitations and optimization of microbial growth (Saadat *et al.* 2020a). In this context, our results here suggest this improvement by linking the active ion flux to heat flux across cellular outer membranes.

Experimental validation of our results is also found in the review (von Stockar 2010), where thermodynamics was applied to simulate living microbial cultures and explore their possible practical use. A study of the energy dissipation effects in industrially fermented cultures, both in terms of heat and Gibbs energy dissipation, has been developed by considering experimental techniques for calorimetric measurements, with particular regards to their use for monitoring and control. The analysis of the dissipation of Gibbs free energy, in chemotrophic growth, is a consequence of both accounting for the irreversibility

(analytically represented by the entropy production) by metabolic processes in the cells and the driving force (energy sources of the biological processes), for growth and metabolism. Using experimental measurements from growth experiments involving a variety of microbial strains, our model predicts that the driving force for growth and metabolism decreases as the growth yield increases. It was proven that the Gibbs function and metabolic process rates are inversely proportional.

The modeling results obtained here suggest a predictive and novel tool for metabolic pathway optimization to improve the techno-economics and efficiency of photosynthetic bio-refineries (Zhu *et al.* 2020). Our results also suggest future studies on the relationship between optimal external temperature and pH and/or fundamental outer membrane properties for biomass growth, division, metabolism, and biofuel and bioplastic production. Indeed, a variation in metabolite exchanges across microbial outer membranes is related to the change of ion concentration and, consequently, to the pH gradient (Dianursanti and Santoso 2015). Therefore, a proposed immediate application of our model is the simulation of co-cultivation of two different microbial species, which can enhance intracellular accumulation of lipid biomolecules for biodiesel production (Rashid *et al.* 2019). Several studies have investigated the co-cultivation of different micro-organisms to improve their lipid concentration. For instance:

- in Ref. (Ling *et al.* 2014), the species *Chlorella pyrenoidosa* and *Rhodospiridium toruloides* were co-cultivated, obtaining $4.60 \text{ g}_{\text{lipid}} \text{ L}^{-1}$ (compared respectively to $3.00 \text{ g}_{\text{lipid}} \text{ L}^{-1}$ and $3.40 \text{ g}_{\text{lipid}} \text{ L}^{-1}$, respectively for each single species);
- in Ref. (Xue *et al.* 2010), the species *Arthrospira platensis* and *Rhodotorula glutinis* were co-cultivated, obtaining $0.467 \text{ g}_{\text{lipid}} \text{ L}^{-1}$ (compared respectively to $0.013 \text{ g}_{\text{lipid}} \text{ L}^{-1}$ and $0.135 \text{ g}_{\text{lipid}} \text{ L}^{-1}$ for the single species);
- in Ref. (Papone *et al.* 2012), the species *Chlorella sp.* and *Toluraspore* were co-cultivated, obtaining $2.42 \text{ g}_{\text{lipid}} \text{ L}^{-1}$ (compared respectively to $0.052 \text{ g}_{\text{lipid}} \text{ L}^{-1}$ and $1.141 \text{ g}_{\text{lipid}} \text{ L}^{-1}$ for the single species);
- in Ref. (Zhao *et al.* 2014), the species *Chlorella sp.* and *Monoraphidium sp.* were co-cultivated, obtaining an improved lipid productivity of $29.52 \pm 1.13 \text{ mg}_{\text{lipid}} \text{ L}^{-1} \text{ d}^{-1}$ (compared respectively to $17.99 \pm 3.39 \text{ mg}_{\text{lipid}} \text{ L}^{-1} \text{ d}^{-1}$ and $17.70 \pm 1.19 \text{ mg}_{\text{lipid}} \text{ L}^{-1} \text{ d}^{-1}$ for the single species).

Our model's results regarding the influence of environmental temperature are also validated by the following previous studies (Ramos *et al.* 1976; Felle *et al.* 1980; Zheng and Trudeau 2015; Stratford *et al.* 2019): the biomass concentrations (cell dry weights) results for ethanol $3.43 \pm 0.08 \text{ g L}^{-1}$ and acetate $0.93 \pm 0.12 \text{ g L}^{-1}$ *Clostridium carboxidivorans* at 37°C (Shen *et al.* 2020), higher than at 25°C , (ethanol $1.58 \pm 0.03 \text{ g L}^{-1}$ and acetate $0.61 \pm 0.15 \text{ g L}^{-1}$ (Shen *et al.* 2020)).

Authors' contributions

Conceptualization, U.L. and G.G.; methodology, U.L., P.W. and G.G.; software, G.G.; validation, U.L., D.F., P.W. and G.G.; formal analysis, U.L.; investigation, G.G.; resources, U.L. and D.F.; data curation, U.L. and G.G.; writing-original draft preparation, U.L., D.F. and G.G.; writing-review and editing, U.L., D.F. and G.G.; visualization, G.G.; supervision,

U.L., D.F. and P.W.; project administration, U.L. and D.F.; funding acquisition, U.L. and D.F. . All authors have read and agreed to the published version of the manuscript.

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