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Similarities of Modulation by Temperature and by Electric Field

Gyula Vincze, Andras Szasz

Department of Biotechnics, Szent István University, Godollo, Hungary
Email: biotech@gek.szie.hu

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Abstract

Glycolytic oscillation is one of the first observed and described nonlinear phenomena in living objects. Our recent paper points out the similarity of the temperature and outer electric field to influence this oscillation. The electric field is absorbed and changes the molecules. Similarly to the effect of heating, molecules have various structural, dynamical and chemical changes promoted by electric field. The changes sometimes happen without increasing the temperature. Temperature, as the average energy of the included particles, has various kinds of "waste" energy used to heat up the particles which do not participate in the desired changes. The inaccuracy of the effects of temperature growth in local molecular changes could be remarkably high and could be corrected by the well-applied electric field absorption.

Keywords

Glycolytic Oscillation, Modulation, Electric Field, Temperature, Electric-Polarization

1. Introduction

Glycolytic oscillation was observed first in yeast suspension by pulsing-addition of glucose to the system [1], registering the transient oscillation of concentration of NAD (Nicotinamide-Adenine Dinucleotide [reduced form]). Cells were studied under anaerobic conditions and oxygen addition terminated the transient oscillation phenomenon. Soon, many biochemical oscillations were measured, [2] [3] pushing the process into the front of the non-linear reaction-kinetics described by ordinary differential equations [4]. This activity accelerated when the first glycolytic oscillation was explained strictly on a mathematical basis called Selkov's model [5]. This bifurcation-based phenomenon soon reached its direct biomedical applications too [6], mainly centered on the pancreatic activity [7].

Mathematical models (like [8]) had great support by the more and more precise experiments [9] [10]. Presently, precise metabolic activity in cells is measured by showing entrainment of heterogeneous glycolytic oscillations in single cells [11] [12], in which work was one of the vast news of the year. Interaction of glycolysis with external electric field stimulation has been known for a long time [13] [14] [15]. Our objective is to clear the following question in detail: are there any similarities between the temperature stimuli and electric stimuli in transient glycolytic oscillation?

2. Method

Temperature is a trivial driving parameter of glycolysis [16] [17]. It was widely investigated experimentally [18] and explained theoretically too [19] as further-developed Selkov's model. Two factors were introduced for this study: a constant α for positive feedback catalytic effect and a $\beta(T)$ for temperature dependence.

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= \nu - \alpha x - \beta(T)xy^2,\\ \frac{\mathrm{d}y}{\mathrm{d}t} &= -wy + \alpha x + \beta(T)xy^2\end{aligned} \tag{1}$$

where ν, α and w are constants, while $\beta(T)$ satisfies the Arrhenius-dependence of temperature.

$$\beta(T) = \beta_0 \mathrm{e}^{-\frac{E}{kT}} \tag{2}$$

Solving these equations, the results were as follows:

1) The average concentration of the reagents decreases by time.

2) The frequency of oscillation depends on the temperature by Arrhenius function.

3) The form of oscillation changes by the temperature.

4) Oscillation can be modulated by the periodic changing of the temperature.

Let us suppose that the activation energy in Arrhenius law depends on the electric field which can have strong synergy with the temperature [20].

Giving the perturbation of the temperature

$$T(t) = T_0 + \Delta T(t), \quad \max|\Delta T| \ll T_0 \tag{3}$$

after a Taylor-expansion and stop at the linear term:

$$\beta(\Delta T(t)) = \beta_0 \mathrm{e}^{-\frac{E}{kT_0}} \mathrm{e}^{\frac{E}{kT_0^2}\Delta(t)} \cong \beta_0 \mathrm{e}^{-\frac{E}{kT_0}} \left(1 + \frac{E}{kT_0^2}\Delta T(t)\right) \tag{4}$$

When the $\Delta E(t)$ changes have periodic part, then:

$$\beta(\Delta E) = \beta_0 \mathrm{e}^{-\frac{E_0+\Delta E(t)}{kT}} = \beta_0 \mathrm{e}^{-\frac{E_0}{kT}} \mathrm{e}^{-\frac{\Delta E(t)}{kT}} \cong \beta_0 \mathrm{e}^{-\frac{E_0}{kT}} \left(1 - \frac{1}{kT}\Delta E(t)\right) \tag{5}$$

If P is the polarization and $\Delta\mathcal{F}(t)$ is the electric field strength, then $\Delta E(t) = -P\Delta E(t)$ and consequently

$$\beta\left(\Delta E(t)\right)=\beta_0 \mathrm{e}^{-\frac{E_0+\Delta E(t)}{kT}}=\beta_0 \mathrm{e}^{-\frac{E_0}{kT}} \mathrm{e}^{-\frac{\Delta E(t)}{kT}} \cong \beta_0 \mathrm{e}^{-\frac{E_0}{kT}}\left(1+\frac{P}{kT}\Delta\mathcal{F}(t)\right) \quad (6)$$

Comparing (4) and (6), the effects which we promote by temperature could be constructed on the same way by electric field, making substitution.

$$E\Delta T \leftrightarrow P\Delta\mathcal{F}(t)$$

3. Discussion

Comparing (4) and (6), electric field has a formally similar effect on the modulation of glycolytic oscillations to the temperature. Driving force is the change of the field strength $\Delta\mathcal{F}(t)$ (instead of the $\frac{\Delta T(t)}{T_0}$ relative temperature change), and chemical activation energy is replaced simply by the polarization of the material. The abovementioned similarity is based on the Arrhenius equation which is a general expression for the temperature dependence of chemical reaction rates, so in the simple empirical comparison of the reaction kinetics it allows the interchange of the temperature and electric field effects. So, the effect is formally similar, but their real action is different, the electric field needs polarizability of the materials which is not the condition for temperature. The glycolysis is a special effect involving the membranes (cytoplasmic and mitochondrial) which have a definite and well distinguishable polarization vector. This means that this similarity makes high parallel effects nearby the membrane of the cells. In the other chemical mechanisms of the living material the difference between the temperature effect and the electric fields is simply the mechanism which these effects induce in the process.

The electric field in this meaning makes equivalent changes in the chemical effects of glycolytic oscillations like temperature does when the heat-exchange is concentrated on a certain chemical reaction and not spread all over the target.

Heat spreads in the target by various convection and conduction effects. Therefore temperature rise in this case cannot be equal to the precisely concentrated electric filed for chemical changes. This is indispensable for making hyperthermia treatment precise, where the accurate approximation of the chemical changes is blocked by the spreading of the heat energy. According to the Pennes Equation [21] [22]:

$$\rho c\frac{\partial T}{\partial T}=div\left(\kappa gradT\right)+h_m+h_b+Q_s(x,t)+Q_D(x,t)$$

where

$$\begin{aligned}\rho c\frac{\partial T}{\partial t}&=div\left(\lambda gradT\right)+\rho_b c_b w\left(T-T_b\right)+p_e\\&=T\left(c_1-c_{11}\zeta_1\right)\frac{\partial\zeta_1}{\partial t}+Tc_2\frac{\partial\zeta_2}{\partial t}=-h_m-Q_s(x,t)\end{aligned} \quad (7)$$

The electric energy source has modified the Pennes Equation, and the changes are realized in reactions (introduced reaction coordinates $\zeta_i\,(i=1,2)$.

$$\rho c\frac{\partial T}{\partial t}+T\left(c_1-c_{11}\zeta_1\right)\frac{\partial \zeta_1}{\partial t}+Tc_2\frac{\partial \zeta_2}{\partial t}-div\left(\lambda gradT\right)$$
$$-\rho_b c_b w\left(T-T_b\right)=p_e \tag{8}$$

Moreover, two extra reaction-equations made the description valid for the system, where reactions could occur.

$$\frac{\mathrm{d}\zeta_1}{\mathrm{d}t}=-\frac{1}{\tau}\left(\zeta_1-\zeta_{1e}\right),$$
$$\frac{\mathrm{d}\zeta_2}{\mathrm{d}t}=L_{22}c_2, \tag{9}$$

This interconnected (coupled) equation-system must be solved for describing the system. A more straightforward form of the conventional system is:

$$\rho c\frac{\partial T}{\partial t}+T\left(c_1-c_{11}\zeta_1\right)\frac{\partial \zeta_1}{\partial t}+TL_{22}c_2^2-div\left(\lambda gradT\right)+\rho_b c_b w\left(T-T_b\right)=p_e,$$
$$\frac{\mathrm{d}\zeta_1}{\mathrm{d}t}=-\frac{1}{\tau}\left(\zeta_1-\zeta_{1e}\right) \tag{10}$$

If the initial condition was zero product (best assumption) then the solution of the second equation is:

$$\zeta_1=\zeta_{1e}\left(1-\mathrm{e}^{-\frac{t}{\tau}}\right) \tag{11}$$

where the saturated (equilibrium) value and the time-constant could be temperature dependent functions. The generalized Pennes Equation with these mathematical treatments:

$$\frac{\partial T}{\partial t}-\frac{\lambda}{\rho c}\Delta T+\frac{\rho_b c_b w}{\rho c}T=\frac{p_e+\rho_b c_b w}{\rho c}T_b-\frac{TL_{11}c_1^2}{\rho c}\mathrm{e}^{\frac{-2t}{\tau}}-\frac{TL_{22}c_2^2}{\rho c}$$
$$\rightarrow\frac{\partial T}{\partial t}-\frac{\lambda}{\rho c}\Delta T+\alpha T=g-N\left(T\right),$$
$$g=\frac{p_e+\rho_b c_b w}{\rho c}T_b,$$
$$N\left(T\right)=\frac{TL_{11}c_1^2}{\rho c}\mathrm{e}^{\frac{-2t}{\tau}}+\frac{TL_{22}c_2^2}{\rho c}, \tag{12}$$
$$\alpha=\frac{\rho_b c_b w}{\rho c},\ L_{11}=\frac{\Lambda_1\mathrm{e}^{\frac{\mu}{RT}}}{R},\ L_{22}=\frac{\Lambda_2\mathrm{e}^{\frac{\mu}{RT}}}{R}$$

The Pennes Equation formally could be rewritten as follows;

$$L\left(T\right)=g \tag{13}$$

where L is a linear differential-operator and g the inhomogeneity term, constructed from the blood-perfusion and the introduced electric-power. If chemical reactions (cellular disruptions) additionally happen, that makes non-linearity to the equation, and the original Equation (13) will be modified:

$$L\left(T\right)+N\left(T\right)=g \tag{14}$$

where N(.) term contains the non-linearities. In a general form Equation (14)

could be:

$$L(T)+\lambda N(T)=g \tag{15}$$

where λ is an arbitrary parameter. (Naturally (14) and (15) are identical if $\lambda=1$).

The solution of (15) could be approached by perturbation approximation having a power-series of λ:

$$T=T_0+\lambda T_1+\lambda^2 T_2+\cdots \tag{16}$$

Because $L(.)$ is linear than:

$$L(T)=\sum_{i=0}^{\infty}\lambda^i L(T_i) \tag{17}$$

However, $N(.)$ is an analytical function of T; consequently, it could be presented as a series of λ powers.

$$N\left(T_0+\lambda T_1+\lambda^2 T_2+\cdots\right)=N(T_0)+\lambda N_1(T_0,T_1)+\lambda^2 N_2(T_0,T_1,T_2)+\cdots \tag{18}$$

Moreover, using these series in the Equation (15) grouping the terms by the power of λ as well as using the arbitrariness of λ, we get:

$$L(T_0)=g,\ L(T_1)=-N(T_0),\ L(T_2)=-N_1(T_1) \tag{19}$$

Solved and substituted to Equation (16) we have the solution of Equation (14) at $\lambda=1$:

$$T=T_0+T_1+T_2+\cdots \tag{20}$$

The T_0 is the ordinary solution of the usual Pennes Equation, and the further terms are the consequences of the non-linear extension, so these are the essentials in our approach.

Let us study the one-dimensional case at first. The one-dimensional Pennes Equation with neglecting of the thermal conduction, using Equation (12):

$$\begin{aligned} L(T)&=\frac{\mathrm{d}T}{\mathrm{d}t}+\alpha T=\frac{p+\rho_b w_b c_b T_b}{\rho c}=g,\\ \alpha&=\frac{\rho_b w_b c_b}{\rho c} \end{aligned} \tag{21}$$

which has a solution:

$$\begin{aligned} T_0&=T_{00}\mathrm{e}^{-\alpha t}+\int_0^t \mathrm{e}^{-\alpha t}\mathrm{e}^{\alpha t^1} g(t')\mathrm{d}t\\ T_{00}&=36.5+273^{\circ}\mathrm{C} \end{aligned} \tag{22}$$

If the electromagnetic power is constant (not time-dependent), then:

$$\begin{aligned} T_0&=T_{0\infty}-(T_{0\infty}-T_{00})\mathrm{e}^{-\alpha t},\\ T_{0\infty}&=\frac{g}{\alpha},\\ T_{00}&=36.5+273^{\circ}\mathrm{C} \end{aligned} \tag{23}$$

Naturally, g could depend on the space-vector so T_0 as well.

The first term of the perturbation solution by (19) is the solution of the fol-

lowing equation:

$$L(T_1)=\frac{\mathrm{d}T_1}{\mathrm{d}t}+\alpha T_1=-N(T_0) \tag{24}$$

Its solution (because the initial condition has been satisfied before) is:

$$T_1=-\int_0^t \mathrm{e}^{-\alpha t}\mathrm{e}^{\alpha t'}N\left[T_0(t'),t'\right]\mathrm{d}t', \tag{25}$$

Substitute N(.) from Equation (12) we have:

$$\begin{aligned}T_1=-\int_0^t \mathrm{e}^{-\alpha t}\mathrm{e}^{\alpha t'}\Bigg[&\frac{T_0(t')L_{11}\left(T_0(t')\right)c\left(T_0(t')\right)_1^2}{\rho c}\mathrm{e}^{\frac{-2t'}{\tau(T_0(t'))}}\\&+\frac{T_0(t')L_{22}\left(T_0(t')\right)c\left(T_0(t')\right)_2^2}{\rho c}\Bigg]\mathrm{d}t',\end{aligned} \tag{26}$$

We only have numerical possibility to solve this, although it has no great importance. We must have the stationery solution, which is enough for hyperthermia conditions.

In stationery cases, T_0 is constant in time, and the first term of the integrands is zero, so:

$$T_1=-\int_0^t \mathrm{e}^{-\alpha t}\mathrm{e}^{\alpha t'}\frac{T_0L_{22}(T_0)c(T_0)_2^2}{\rho c}\mathrm{d}t'=-\frac{T_0L_{22}(T_0)c(T_0)_2^2}{\alpha\rho c}\left(1-\mathrm{e}^{-\alpha t}\right), \tag{27}$$

where the only stationer solution is:

$$T_1=-\frac{T_0L_{22}(T_0)c(T_0)_2^2}{\alpha\rho c} \tag{28}$$

What did we get for the value of the temperature correction?

Nothing on the absolute value, because no experimental data exists. However, the relative change could be guessed by the experimental dose-function.

The correction at 43˚C for arbitrary T temperature, based on the Equation (28), is:

$$\frac{T_{1T}}{T_{143}}=\frac{T_{0T}}{T_{043}}\frac{L_{22}(T)c(T)_2^2}{L_{22}(T_{43})c(T_{43})_2^2}\frac{\rho cw_{b43}}{\rho cw_{bT}} \tag{29}$$

Using the results from the dose-idea:

$$t_{eq}=\frac{L_{22}c_2^2\big|_{T=T_{43}}}{L_{22}c_2^2\big|_T}t:=R^{(T_{43}-T)}t \tag{30}$$

where according to Sapareto and Dewey [23]:

$$R=\begin{cases}0, & \text{if } T<3^{\circ}\mathrm{C}\\ 0,25, & \text{if } 39^{\circ}\mathrm{C}\le T<43^{\circ}\mathrm{C}\\ 0,5, & \text{if } T\ge 43^{\circ}\mathrm{C}\end{cases} \tag{31}$$

Based on these equations:

$$\frac{T_{1T}}{T_{143}} = \frac{T_{0T}}{T_{043}} \frac{\rho c w_{b43}}{\rho c w_{bT}} \frac{1}{R^{(T_{43}-T)}} \tag{32}$$

For example, when we compare two temperature points: $T_{41} = 273 + 41 = 314$ K, and $T_{45} = 273 + 45 = 318$ K. In the first interval (41˚C - 43˚C) $R_{41} = 0.25$ and the second: (43˚C - 45˚C) $R_{45} = 0.5$. The blood-perfusion rate at T_{41} $w_{b41} = 20$ ml/min/100g, and at T_{45} is w_{b45} 5 ml/min/100g [24].

Then the ratio of corrections according to Equation (32) is

$$\begin{aligned} \frac{T_{141}}{T_{143}} &= \frac{T_{041}}{T_{043}} \frac{w_{b43}}{w_{b41}} \frac{1}{R_1^{(T_{43}-T_{41})}}, \\ \frac{T_{145}}{T_{143}} &= \frac{T_{044}}{T_{043}} \frac{w_{b43}}{w_{b45}} \frac{1}{R_2^{(T_{43}-T_{45})}} \end{aligned} \tag{33}$$

where

$$\frac{T_{141}}{T_{145}} = \frac{T_{041}}{T_{045}} \frac{w_{b45}}{w_{b41}} \frac{R_2^{(T_{43}-T_{41})}}{R_1^{(T_{43}-T_{45})}} == \frac{314}{318} \frac{5}{20} \frac{0.5^{-2}}{0.25^2} \cong 16 \tag{34}$$

This means if at temperature 45˚C we have an inaccuracy $\Delta T_{45C} = 0.2$˚C due to the chemical reactions, then the correction on $T = 41$˚C became $\Delta T_{41C} = 3.2$˚C. Due to the general hyperthermia practice, the temperature does not exceed the 41˚C in average, so the inaccuracy in these practical temperatures is large. The application of electric field enhances the accuracy to target the chemical bonds directly. Consequently, this energy-absorption has better efficacy at the same temperature when applied according to the targeted bonds. General electromagnetic radiation or capacitive heating affects all dipoles, not only the concentration for those which are devoted for cellular destruction. This is the reason why certain cell-destruction can occur at a lower temperature [25] [26], when precise impedance-matched electric field action is applied, [27].

4. Conclusion

Modulation of the glycolysis both by temperature and external field is feasible. The values of the reaction change depend on the temperature and field changes by activation energy multiplied by change of temperature, and by the polarization multiplied by the change of the field. The electric field has a similar dynamic change to heating. Temperature, as the average energy of the included particles has various "waste" energy used to heat up the particles which do not participate in the desired changes. The various molecular changes in their spatiotemporal structure and the dynamical, geometrical, chemical changes could be promoted by electric field without increasing the temperature. The inaccuracy of the temperature effect could be high and must be corrected by the well-applied, electric field application.

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