Model-based analysis of hypothalamus controlled fever: the non-equilibrium thermodynamic aspect

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Abstract

We focus on the symptom of hypothalamus controlled fever, which is in fact a problem related to non-equilibrium system. Since live human body has constant temperature, whose dissipation is easy to be figured out by observation, it is a suitable candidate for non-equilibrium system to study. In our paper, human body is regarded as a 2-compartment-system: one is the chemical-reaction network, the other is observed by mechanical motion which means the vital signs apart from body temperature. Van der Pol model is used to describe the overall effect of chemical reaction network in human body. When the parameter of mathematical model is set to guarantee the mathematical model to be in limit cycle oscillation state, the energy absorbtion and releasing is computed. With the help of body temperature, which can be observed, the energy metabolism of overall effect of chemical reaction network is figured out. We have figured out the conditions when human is at healthy and fever how the mathematical respond. This response is just the overall effect of chemical reaction network. This research may be capable of answering the question whether fever is a kind of illness or some response of body to maintain its life? From our study, hypothalamus controlled fever is beneficial to maintain life.

KEYWORDS: Non-equilibrium, Fever, Limit cycle, Lyapunov function

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1 Introduction: Motivation and approach

Fever is a kind of symptom caused by several reasons: infectious disease, immunological diseases, metabolic disorders and so on [1]. For convenience, we are to use fever to denote both the sickness fever and symptom febrile in the following passage. The cause of fever can be divided into 2 kinds [1]:

hypothalamus controlled, and non-hypothalamus controlled. The former is the case which we are interested in. Fever is a symptom related to many kinds of sickness [1,2]. It is after some diagnosis that one can understand what kind of sickness causes the symptom. Physiologists have already studied fever by experiment. Whether fever is beneficial, different researchers have different opinions. Sometimes their opinions are controversial [3, 4]. In this paper, we tried a different approach to answer whether fever is beneficial. Even though fever has been studied for quite a long time, because of the complexity of human body, the confident results of experimental study are limited [2]. While body temperature is one of the important vital signs [5], the result of our study is of importance to clinical doctors.

We use mathematical method to study physiology. Mathematical physiology can be dated back to last century [6]. In this point of view, human body is in fact a complex network with chemical reaction, immune and nervous system. The most basic network is the chemical reaction network [7]. Though human body system is complex, it is still possible to use limited vital signs to describe life. Inspired by this method in medical science and the approach in mathematical physiology, though the chemical reaction network is extremely complex, still its regulation is periodic and stable, and is possible to use 2 variables to describe [8, 9]. That is, the overall effect of chemical reaction network is in fact a limit cycle [6]. Similarly, the cardiac rhythmicity is also a stable limit cycle [6]. According to the knowledge of physiology, cardiac rhythmicity is relevant to respiration rate [5]. The vital signs apart from body temperature is oscillating at a certain interval, because of the limit cycle mechanism.

In view of mathematical physiology, hypothalamus controlled fever is regarded as the perturbation of limit cycle system [10] or some regulation of parameter of limit cycle system. Any stable limit cycle has the property of stability and periodicity [11, 12]. These properties implies that it is possible to use a simpler limit cycle model. In this paper we are to use 2 variables (q_1, q_2) whose evolution orbit is a limit cycle to describe the overall effect of chemical reaction network.

On the other hand, with the help of physics, a living human body is a typical system far from equilibrium, with energy exchange from environment [13]. And its temperature is kept constant. It is not difficult to figure out energy dissipation per unit time of systems with constant temperature [14–18]:

$$\begin{aligned} \frac{d}{dt}E_D &= T_b\frac{d_i s}{dt} \\ &= -T_b\kappa\bigtriangledown T(T_b^{-1} - T_{en}^{-1})\sigma \end{aligned} \tag{1.1}$$

in which E means energy and the subscript D denotes dissipation. T for temperature the subscript b denotes body, and the subscript en denotes environment. Most of the time $T_{en} < T_b$. σ is the cross-sectional area, as it is a unit area, we set $\sigma = 1$. $\kappa > 0$ is thermal conductivity constant. According to Fourier's law, this leads to constant thermal flux. $\frac{d_i s}{dt}$ is the entropy production rate of unit volume. (1.1) gives constant entropy production rate.

Any dissipative system has a source [16–18]. For the system we study, the source is just the chemical reaction network [7]. Divide the human body system into 2 compartments: one is observable, the other is unobservable. The former is observed by vital signs such as body temperature, pulse or blood pressure, the latter is given by some mathematical model consists 2 variables such as (q_1, q_2), which are used to describe the overall effect of chemical reaction network. The human body system absorbs substance from environment. Substance is changed into energy by chemical reaction network. Part of the energy is detected by vital signs, such as pulse, and the other part is related to dissipation which can be detected by body temperature [5]. This way of thinking provides us approach to study the symptom of hypothalamus controlled fever. The following sections will follow this approach in detail.

Before moving on let us give the organization of this paper: In section2, we proposed the calculation principal. In section 3.1 we explained the reason why we choose limit cycle model (3.1) to be the mathematical model and used a working function (7.4) to figure out the energy absorbtion and releasing. In section 3.2, we found the Lyapunov function of (3.1). In section 4, we analyzed the 2 cases: healthy and fever. We found the response of mathematical model (3.1) to the 2 cases.

2 Balance of energy

Following the proposal in section 1, the human body system consists of 2 parts: observable part and unobservable part. The observable part is related to vital signs, the unobservable part is related to overall effect of chemical reaction network. The time scale of chemical reaction in human body is much smaller than that of macroscopic motion [5, 6, 19]. Or the energy produced by chemical reaction can not support human body's macroscopic motion sustainedly.

Define 2 symbols div_+, div_- to be proportional to available energy (related to pulse, respiration etc) and energy absorbed in an oscillation period, and let τ be the oscillation period of system (q_1, q_2) which is the period of overall effect of chemical reaction network. The energy absorbed from environment is proportional to div_-, part of which is changed into available energy proportional to div_+ i.e. $div_+ \propto dE_k$. The subscript k denotes kinetic energy which is available. In the period τ, the energy that can not be converted into available energy is changed into thermal energy which can be observed by body temperature. This means that the difference between available energy and energy absorbed which changes into thermal energy. Correspondingly, $(|div_-| - |div_+|) \propto dE_D$. Since the time scale of chemical reaction network is much smaller, it is reasonable to assume that in a oscillation period, the difference of energy absorbtion and releasing is proportional to the macroscopic system's energy dissipation rate. Then:

$$\frac{1}{\tau}(|div_-| - |div_+|) \propto -T_b \kappa \bigtriangledown T(T_b^{-1} - T_{en}^{-1})\sigma \tag{2.1}$$

here we assume the scale that $\tau \sim dt$. The reason why we use the symbol proportional to rather than equal to is that the model of system (q_1, q_2)'s dimension might be different from energy.

Next step is to construct a mathematical model to compute the exact expression of $div_\pm$, and get the exact relation between $div_\pm$ and energy. The dimension of $|div_-| - |div_+|$ can be removed by some constant such as β. Using (2.1) we get:

$$\frac{kT_b}{\beta}\frac{1}{\tau}(|div_-| - |div_+|) = \frac{d}{dt}E_D \tag{2.2}$$

β is a coefficient guarantees $\frac{(|div_-|-|div_+|)}{\beta}$ dimensionless. k is Boltzmann constant. In practice, we use the explicit expression of (1.1) like this

$$\frac{d}{dt}E_D = -T_b\frac{T_{en} - T_b}{T_{en}T_b}\kappa\frac{T_b - T_{en}}{\Delta r} \tag{2.3}$$

For instance axillary temperature is $T_b = 310.15K$, and the environmental temperature $T_{en} = 298K$. Δr is the thickness of air layer (in fact very thin) [20, 21], which means the distance Δr from armpit.

Next section, we are to use a mathematical model to describe the overall effect of chemical reaction network, in order to get $div_\pm$.

3 Mathematical model: description of overall effect of chemical reaction network

Our assumption is that the overall effect of chemical reaction network system is in fact phenomenologically modeled by a 2-variable limit cycle [5–7] and any limit cycle model is attractive and periodic. Lots of research work has been done to analyse limit cycle, which is dated back to the middle of last century [22, 23]. In this paper we only use a simplest and typical limit cycle model called Van der Pol model [24] as an example to show how to use double variable system to estimate the energy produced by the huge chemical reaction network of human body.

3.1 Van der Pol model

In this section, readers should bear in mind that the time scale for overall effect of chemical reaction network is much smaller than the macroscopic world. We should have used another alphabet to substitute the parameter t. However, it is conventional to use t to be the time variable, so we use also t, but it has much smaller time scale than that in (1.1). The Van der Pol model is given below [24]:

$$\begin{aligned} \dot{q}_1 &= -q_2 \\ \dot{q}_2 &= \omega^2 q_1 + \mu(1 - q_1^2)q_2 \end{aligned} \tag{3.1}$$

in which q_1 and q_2 are thermodynamic variables, and μ is the parameter externally controlled. ω is the oscillation frequency if $\mu = 0$. It is conventional to set $\omega = 1$ convenience.

Most of the time, searching for limit cycle is by qualitative linearized stability analysis (see 7.1) and numerical calculation, but it can not give the analytical information of limit cycle. To get the analytical information, we need to analyse the vector field in phase space. System (3.1) forms a vector field in phase space (q_1, q_2). Directly we can compute the divergence of (3.1):

$$div = \frac{\partial \dot{q}_1}{\partial q_1} + \frac{\partial \dot{q}_2}{\partial q_2} = \mu(1 - q_1^2) \tag{3.2}$$

One can immediately notice that (3.2) can be both positive and negative depending on the value of q_1. If the exact solution of (3.1) is got, we can figure out $div_\pm$ by integrating along the orbit in phase space:

$$div_+ = 2\int_{q_1=-1,q_2(q_1=-1)}^{q_1=1,q_2(q_1=1)} ds \quad div(s) \tag{3.3}$$

$$div_- = 2(\int_{q_2=0,q_1(q_2=0)>0}^{q_1=1,q_2(q_1=1)} ds \quad div(s) + \int_{q_1=-1,q_2(q_1=-1)}^{q_2=0,q_1(q_2=0)<0} ds \quad div(s)) \tag{3.4}$$

$div_\pm$ are exactly those in (2.1) mentioned in section 2. The reason why we multiply the above integration by 2 is that as the symmetry of (3.1), integration path only covers half of the limit cycle. When the shape of limit cycle is got, explicit form of $div_\pm$ is figured out. In mathematical language, limit cycle is a limit set for dynamic system. In physics language, it is a thermodynamic limit. Thermodynamic property in physics corresponds to Lyapunov function in mathematics. It is quite natural to construct a function $V(q_1, q_2)$, such that [25]

$$\frac{d}{dt}V(q_1, q_2) = \frac{\partial V(q_1, q_2)}{\partial q_1}\dot{q}_1 + \frac{\partial V(q_1, q_2)}{\partial q_2}\dot{q}_2 \tag{3.5}$$

If $\frac{d}{dt}V(q_1, q_2)$ does not change sign, then $V(q_1, q_2)$ is Lyapunov function. In particular, $\frac{d}{dt}V(q_1, q_2) \leq 0$ the limit set is the $\omega-$limit set [12], i.e. system is stable at long time limit.

(3.1) is a Hamiltonian system if $\mu = 0$. According to [26–28] system (3.1) consists of 2 parts: Hamiltonian term which is of $O(\mu^0)$ and perturbation term which is of $O(\mu)$. The shape of limit cycle is related to the Lyapunov function:

$$\frac{\partial V(q_1, q_2)}{\partial q_1}\dot{q}_1 + \frac{\partial V(q_1, q_2)}{\partial q_2}\dot{q}_2 = V(q_1, q_2)(\frac{\partial \dot{q}_1}{\partial q_1} + \frac{\partial \dot{q}_2}{\partial q_2}) \tag{3.6}$$

limit cycle is contained in $V(q_1, q_2) = 0$, when $V(q_1, q_2)$ is not the exact form in phase space. Following the steps in reference [26, 27], we just take the first order approximation of the $V(q_1, q_2)$, that is $V(q_1, q_2) = V_0(q_1, q_2) + \mu V_1(q_1, q_2)$. The exact equation is given in appendix 7.1. It is more convenient to use polar coordinate to show the solution of (7.4) explicitly. $q_1^2 + q_2^2$ is the square of radius in (q_1, q_2) plane. Solving (7.4) order by order, the first order explicit solution is

$$\sqrt{q_1^2 + q_2^2} = 2 - 8\mu\cos\theta\sin^3\theta \tag{3.7}$$

by convention $q_1 = \sqrt{q_1^2 + q_2^2}\cos\theta, q_2 = \sqrt{q_1^2 + q_2^2}\sin\theta$. The second term is in fact $8\frac{\mu}{\omega}\cos\theta\sin^3\theta$, and $\omega = 1$. Details are discussed in 7.1. The solution explicitly shows that the distance of each point on the limit cycle to the singular point is $2 - 8\mu\cos\theta\sin^3\theta$. Readers can consult [26] and [27]. Here θ is in fact the re-parametrization of time i.e. $\int_0^\tau dt\theta(t) = 2\pi$. The first order approximation of radius and θ is given by fig.1 with comparison to numerical result.

The period τ which appears in (2.1) is changed into 2π. When $\mu = 0$, $\tau = \frac{2\pi}{\omega} = 2\pi$. The period appears in this paper is proportional to 2π multiplied by a small parameter $\xi \to 0$ with dimension $[t]$ [29], so as to keep the right time scale.

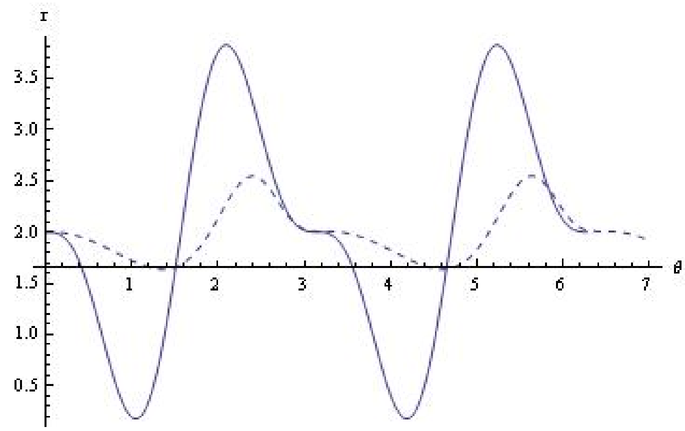

Figure 1: Polar coordinates of the limit cycle's radius and its corresponding parameter θ with $\mu = 0.7$. The dashed line is the numerical result by solving the differential equation, and the true line is the first order approximation

Solutions of the equations below determine θ where makes div changes sign:

$$(2 - 8\mu\cos\theta\sin^3\theta)\cos\theta = 1 \tag{3.8}$$

$$(2 - 8\mu\cos\theta\sin^3\theta)\cos\theta = -1 \tag{3.9}$$

(3.8) and (3.9) are difficult to solve, and the solution shows that θ is in fact the function of μ. Solution of (3.8) is θ_1 and (3.9) is θ_2 in $\theta \in (0, \pi)$ are approximately fitting by the polynomials

$$\theta_1 = 1.05479 - 1.11732\mu + 0.767715\mu^2 - 0.183246\mu^3 \tag{3.10}$$

$$\theta_2 = 2.09199 - 0.655212\mu + 0.673129\mu^2 - 0.279221\mu^3 \tag{3.11}$$

the solution about $\theta \in (-\pi, 0)$ is not necessary, because of symmetry. When $\mu = 0$, $\theta_1 = \frac{\pi}{3}$, and $\theta_2 = \frac{2\pi}{3}$. Details of the numerical result are shown in section7.2. Then $div_\pm$ are

$$\begin{aligned} div_- &= 2\{\int_0^{\theta_1} d\theta\mu[1 - (2 - 8\mu\cos\theta\sin^3\theta)^2\cos^2\theta] \\ &\quad + \int_{\theta_2}^{\pi} d\theta\mu[1 - (2 - 8\mu\cos\theta\sin^3\theta)^2\cos^2\theta]\} \end{aligned} \tag{3.12}$$

$$div_+ = 2\int_{\theta_1}^{\theta_2} d\theta\mu[1 - (2 - 8\mu\cos\theta\sin^3\theta)^2\cos^2\theta] \tag{3.13}$$

The integration is discussed in 7.3. The divergence in a period is represented by μ

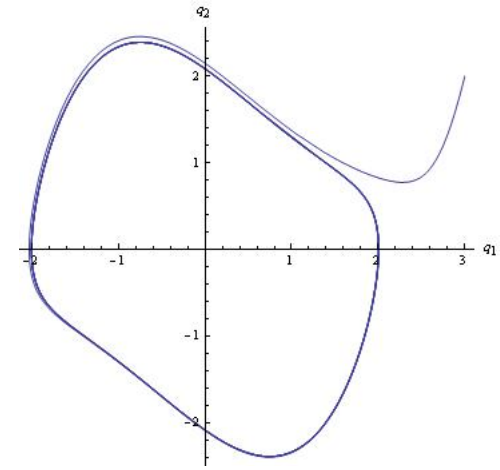

Figure 2: limit cycle of (3.1) numerically depicted with the parameter $\mu = 0.7$ and initial condition $q_1(t_0) = 3, q_2(t_0) = 2$.

$$
\begin{aligned}
|div_-| - |div_+| &= |div_+ + div_-| \\
&= -\int_0^{2\pi} d\theta \mu[1 - (2 - 8\mu\cos\theta\sin^3\theta)^2\cos^2\theta] \\
&= \frac{1}{2}\mu(4 + 3\mu^2)\pi
\end{aligned} \tag{3.14}
$$

In order to check whether 7.4 gives the right result, one can compute the characteristic multipliers of (3.1). Characteristic multipliers reflects the stability of the system. The characteristic multipliers Λ_1, Λ_2 are:

$$
\begin{aligned}
\Lambda_1 &= \frac{\Lambda_1 + \Lambda_2}{2} + \sqrt{\frac{(\Lambda_1 + \Lambda_2)^2}{4} - \exp[\int_0^\tau div(s)ds]} \\
\Lambda_2 &= \frac{\Lambda_1 + \Lambda_2}{2} - \sqrt{\frac{(\Lambda_1 + \Lambda_2)^2}{4} - \exp[\int_0^\tau div(s)ds]}
\end{aligned} \tag{3.15}
$$

in which $div(s)$ is given by (3.2). Details of computing characteristic multipliers (3.15) is shown in appendix 7.4. The final result shows that the real parts of characteristic multipliers are less than 1, which means that the periodic solution of (3.1) is a limit cycle.

Mathematical behavior of system (3.1) when $\mu > 0$ coincides with a biological system: the property of periodicity and stability.

The stability is more directly shown by Lyapunov function. In next subsection, we are to calculate the Lyapunov function in first order approximation.

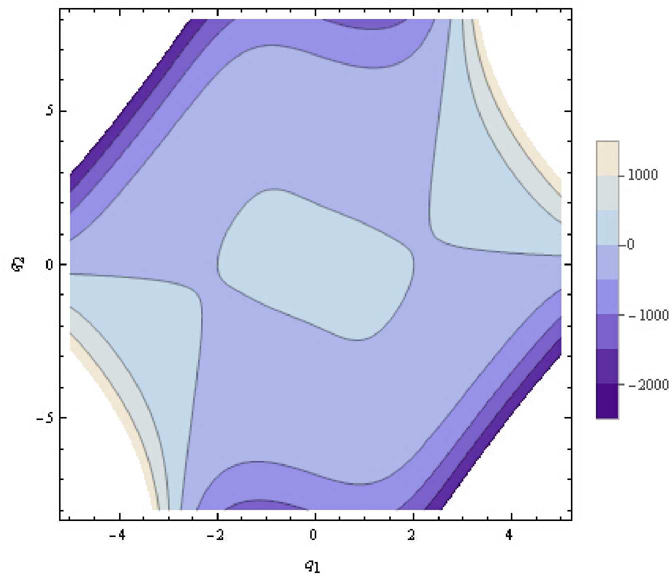

Figure 3: Contour figure of Lyapunov function $V(q_1, q_2)$ in first order approximation with the parameter $\mu = 0.7$

3.2 Lyapunov function of Van der Pol model

Any limit cycle is a limit set, which means that there exists some potential which dominates the evolution. The potential is called the Lyapunov function. Lyapunov function is negative definite when system is tending to steady state. When $V(q_1, q_2) = 0$, it is related to the shape of limit cycle, as we have mentioned in section 3.1. In section 1 we have mentioned the entropy production which is positive definite when the system is tending to steady state. [17] has already pointed out that entropy production plays the role in the thermodynamic system just as Lyapunov function plays the role in dynamical system. Lyapunov function and entropy production are proportional to:

$$- V(q_1, q_2) \propto \frac{d_i s}{dt} \tag{3.16}$$

When entropy production is at steady state i.e. $\frac{d_i s}{dt}$ is constant, $V(q_1, q_2) = 0$.

When the system is perturbed, the orbits in phase space (q_1, q_2) is deviated from the limit cycle, so $V(q_1, q_2)$ equals to some infinitesimal higher order quantity. This perturbation does not change the value of parameter μ. Fig 2 schematically shows that when μ does not change, orbit tends to limit cycle at long time limit. Contour graph of Lyapunov function is shown by Fig 3. Compare fig. 2 with fig 3 one can intuitively find out that the trajectories choose the way which is in the "potential valley".

By solving (7.4), it shows that different value of μ gives different thermodynamic limit, though all these thermodynamic limits are of periodicity and attraction. One may have already noticed that the thermodynamic behavior strongly depends on the parameter μ. When $\mu < 0$ the thermodynamic limit is not a limit cycle, but the singular point $(0, 0)$. When $\mu = 0$, the system turns out to be a harmonic

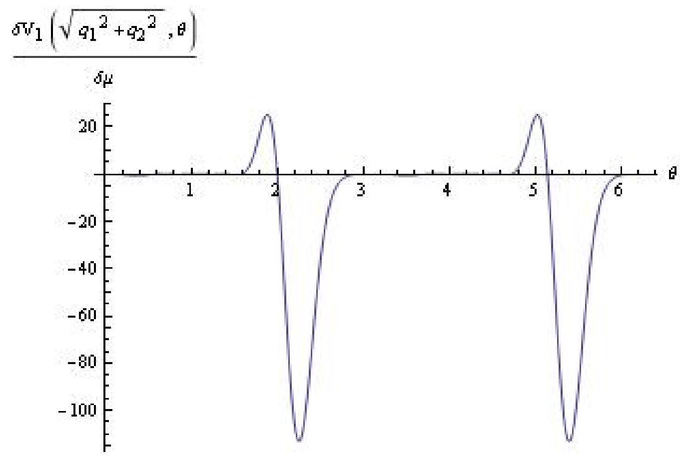

Figure 4: $\frac{\delta V(\sqrt{q_1^2+q_2^2},\theta)}{\delta\mu}$ with the limit cycle constraint in first order approximation with parameter $\mu = 0.9$

oscillator. So the how the parameter μ influences Lyapunov function $\frac{\delta V(q_1,q_2)}{\delta\mu}$ is more crucial than the Lyapunov function itself. $\frac{\delta V(q_1,q_2)}{\delta\mu}$ of (3.1) is:

$$\frac{\delta V(q_1,q_2)}{\delta\mu} = \frac{1}{4}q_1q_2(4-5q_1^2+q_1^4-3q_2^2+q_1^2q_2^2) \tag{3.17}$$

By solving equation (7.4) gives the result that $\frac{\delta V(q_1,q_2)}{\delta\mu}$ expressed by q_1,μ:

$$\begin{aligned}\frac{\delta V(q_1,q_2)}{\delta\mu} = \frac{1}{4}\int_{-\infty}^{\infty} & d\mu\delta(\mu-\mu_0) \\ & \times q_1q_2(q_1,\mu)[4-5q_1^2+q_1^4-3q_2^2(q_1,\mu)+q_1^2q_2^2(q_1,\mu)]\end{aligned} \tag{3.18}$$

In which $\delta(\mu-\mu_0)$ is the Dirac δ-function and μ_0 is the parameter system (3.1) originally chosen. It is more convenient to rewrite (3.18) into polar coordinates:

$$\begin{aligned}\frac{\delta V(\sqrt{q_1^2+q_2^2},\theta)}{\delta\mu} &= \cos\theta\sin\theta(2-8\mu\cos\theta\sin^3\theta)^2 \\ &\quad -\frac{1}{16}(8\sin 2\theta+\sin 4\theta)(2-8\mu\cos\theta\sin^3\theta)^4 \\ &\quad +\frac{1}{4}\cos^3\theta\sin\theta(2-8\mu\cos\theta\sin^3\theta)^6\end{aligned} \tag{3.19}$$

in which $\sqrt{q_1^2+q_2^2} = 2-8\mu\cos\theta\sin^3\theta$ which we have already computed in section 3.1. Schematic pictures are shown by fig.4 and fig.5 as example.

For $\frac{\delta V(\sqrt{q_1^2+q_2^2},\theta)}{\delta\mu}$, the larger the parameter μ, the farther the deviation of variation from 0 in a period. This implies that the larger μ is chosen, the larger $|div_+ + div_-|$. Lyapunov function is the dominate potential which dominates the system's evolution. Just like some thermodynamic function

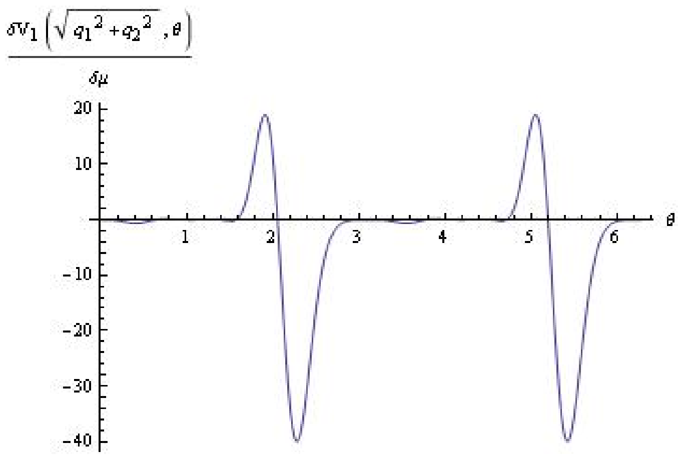

Figure 5: $\frac{\delta V(\sqrt{q_1^2+q_2^2},\theta)}{\delta\mu}$ with the limit cycle constraint in first order approximation with the parameter $\mu = 0.7$

which sustains the system's stability. $\frac{\delta V(\sqrt{q_1^2+q_2^2},\theta)}{\delta\mu}$ directly reflects how the Lyapunov function change with parameter μ. This implies that μ characterizes the state of the system. When the system's structure state is unchanged, μ does not change. Perturbation to the system will disappear at long time limit.

4 Coupling of chemical reaction network to the energy of observable part: physic behind

We assume in section 3.1 that the environmental temperature is unchanged. According to (2.2) we can figure out β:

$$\beta^{-1} = \frac{2\kappa\tau}{N_0 k\mu\pi}(4+3\mu^2)^{-1}\frac{1}{T_{en}T_b}\frac{(T_b - T_{en})^2}{\Delta r} \tag{4.1}$$

in which N_0 is some dimensionless constant such as avogadro constant, considering the entropy production is related to thermodynamics. If human is at quiescent condition, energy dissipation is at minimum.

4.1 Non-quiescent but healthy condition

However human is not always at quiescent condition, as we can not sleep all the day. Healthy human corresponds to our model that the parameter μ is unchanged, so daily exercises is the perturbation to the chemical reaction network. That is, μ remains unchanged and the Lyapunov function

$$V(q_1, q_2) = \widetilde{\epsilon} \tag{4.2}$$

in which $\widetilde{\epsilon} \to 0$, an infinitesimal higher order term. Rewrite the Lyapunov function in polar coordinate and solve (4.2). Since $\widetilde{\epsilon}$ is the perturbation, the system tends to the state which corresponds to

$V(q_1, q_2) = 0$. The evolution to $V(q_1, q_2) = 0$ is limit-cycle-like oscillation state. In 0-th order approximation, it turns out to be

$$[2 - \frac{1}{2}(q_1^2 + q_2^2)]\frac{1}{2}(q_1^2 + q_2^2) = \widetilde{\epsilon} \tag{4.3}$$

it is easy to figure out $\frac{1}{2}(q_1^2+q_2^2) = 1 \pm \sqrt{1-\widetilde{\epsilon}}$, and only $\frac{1}{2}(q_1^2+q_2^2) = 1+\sqrt{1-\widetilde{\epsilon}}$ is of physics meaning. It is more convenient to write $\frac{1}{2}(q_1^2+q_2^2) = 2 \pm \epsilon$ in which $\widetilde{\epsilon} = \mp 2\epsilon - \epsilon^2$. When $\widetilde{\epsilon}$ and ϵ go to 0, they are of the same order. Notice that before being at limit set the system's Lyapunov function is negative definite, so $\widetilde{\epsilon} < 0$ so $\widetilde{\epsilon} = -2\epsilon - \epsilon^2$ and $\frac{1}{2}(q_1^2+q_2^2) = 2+\epsilon$ in which $\epsilon > 0$. When perturbation is added, the solution is:

$$\begin{aligned} \sqrt{q_1^2 + q_2^2} &= 2 - 8\mu\cos\theta\sin^3\theta \\ &\quad -\epsilon\mu(\sin 2\theta - 2\sin 4\theta - 1) \\ &\quad +\epsilon^2\mu(\frac{5}{4}\sin 4\theta - \sin 2\theta) \\ &\quad +\epsilon^3\mu(\frac{1}{2}\sin 2\theta + \frac{1}{4}\sin 4\theta) \end{aligned} \tag{4.4}$$

Because $kT_b\frac{(|div_-|-|div_+|)}{\beta\tau} = \frac{dE_D}{dt}$, the energy dissipation is unchanged in $O(\epsilon^0)$. And in $O(\epsilon)$ and higher order is the extra energy dissipation corresponding to daily exercises. We get dissipation energy is related to (3.14):

$$\frac{dE_D}{dt} = \frac{2\kappa}{k\mu\pi}(4+3\mu^2)^{-1}\frac{1}{T_{en}T_b}\frac{(T_b - T_{en})^2}{\Delta r}(|div_-| - |div_+|) \tag{4.5}$$

To the order of $O(\epsilon)$ approximation the energy dissipation rate, it turns out to be:

$$\frac{dE_D}{dt} = \kappa\frac{1}{T_{en}T_b}\frac{(T_b - T_{en})^2}{\Delta r} + \epsilon\frac{8+3\mu^2}{4+3\mu^2}\kappa\frac{1}{T_{en}T_b}\frac{(T_b - T_{en})^2}{\Delta r} \tag{4.6}$$

the result means that when human is healthy, the energy dissipation apart from quiescent condition is of higher order which does little influence to the quiescent condition energy dissipation. The energy absorbed from the environment and the energy for vital signs apart from body temperature are given by:

$$\frac{kT_b}{\beta\tau}|div_-| = -\frac{2}{\tau}\int_{\theta_1}^{\theta_2} d\theta[...] \tag{4.7}$$

and

$$\frac{dE_k}{dt} = \frac{kT_b}{\beta\tau}|div_-| - \frac{dE_D}{\tau} = \frac{2}{\tau}\int_{\theta_1}^{\theta_2} d\theta[...] \tag{4.8}$$

in which θ_1 and θ_2 are the same as the one in (3.12) and (3.13), because μ does not change. [...] in (4.7) is the integrating term in (3.12) with first order approximation. And [...] in (4.8) is the integrating term in (3.13) with first order approximation. Details of computing (4.7) and (4.8) including the dissipation $\frac{dE_D}{dt}$ are in appendix 7.3.

4.2 Fever and quiescent condition

Now let us come to the case when human is not healthy, that is in this paper, with the symptom of fever. When body temperature increases, and the environment temperature is constant, let $T_{bf} = T_b + \delta T$, in which the subscript f denotes the state fever. Compare entropy production under the 2 cases:

$$\begin{aligned}\frac{d_i s}{dt}(T_{bf}) - \frac{d_i s}{dt}(T_b) &= \frac{\kappa}{\Delta r}[\frac{(T_b + \delta T - T_{en})^2}{T_{en}(T_b + \delta T)} - \frac{(T_b - T_{en})^2}{T_{en} T_b}] \\ &= \frac{\kappa}{\Delta r}\frac{(T_b - T_{en})(T_b + T_{en})\delta T + \delta T^2 T_b}{T_b T_{en}(T_b + \delta T)}\end{aligned} \tag{4.9}$$

As most of the time $T_b > T_{en}$, or the environment is too uncomfortable to live, we can conclude that fever makes energy dissipation increase. We can further compute how the entropy production change with body temperature:

$$\frac{\frac{d_i s}{dt}(T_{bf}) - \frac{d_i s}{dt}(T_b)}{\delta T} = \frac{\kappa}{\Delta r}\frac{(T_b - T_{en})(T_b + T_{en}) + \delta T T_b}{T_b T_{en}(T_b + \delta T)} \tag{4.10}$$

The calculation reveals when body temperature increases, $\frac{d_i s}{dt}(T_{bf}) > \frac{d_i s}{dt}(T_b)$. However, for $\frac{d_i s}{dt}$ is still constant, the only difference is that the constant of T_b and T_{bf} are different. As we have mentioned in section 3.2, correspondingly the Lyapunov function $V(q_1, q_2) = 0$, while the shape of limit cycle changes. For entropy production, the crucial variable is body temperature T_b. For Lypapunov function, the crucial parameter is μ. In section 3.2 (3.19) shows that μ increases $\frac{\delta V(q_1,q_2)}{\delta \mu}$ decreases (absolute value increases) on the whole. This intuitive picture shows that when body temperature increases, the parameter μ also increases. System (3.1) directly related to entropy production is $|div_-| - |div_+|$. So according to (2.1) and (3.14) we get that:

$$\frac{kT_{bf}}{\beta\tau}\frac{\mu(4 + 3\mu^2)\pi}{2} = k\frac{\kappa}{T_{en}}\frac{(T_{bf} - T_{en})^2}{\Delta r} \tag{4.11}$$

As β is just a coefficient to guarantee $\frac{(|div_-| - |div_+|)}{\beta}$ dimensionless, here the calculation just take β as a constant which is figured out at healthy state (4.1), the only cause that makes energy dissipation increase stems from μ, so:

$$\begin{aligned}\beta^{-1}\frac{\partial \mu}{\partial T_b}\frac{(4 + 9\mu^2)\pi}{2} &= \frac{\partial}{\partial T_b}\frac{d_i s}{dt}\tau \\ &= 2\frac{\kappa}{\Delta r}\frac{(T_b - T_{en})(T_b + T_{en}) + \delta T T_b}{T_b T_{en}(T_b + \delta T)}\tau\end{aligned} \tag{4.12}$$

So $\frac{\partial \mu}{\partial T_b}$ is:

$$\frac{\partial \mu}{\partial T_b} = \frac{N_0 k\mu(4 + 3\mu^2)[\delta T T_b + (T_b - T_{en})(T_b + T_{en})]}{(4 + 9\mu^2)\tau T_b^3(\delta T + T_b)(T_b - T_{en})^2} \tag{4.13}$$

It is easy to get the conclusion that $\frac{\partial \mu}{\partial T_b} > 0$, so the parameter μ will increase if body temperature increases. And it is able to show the parameter μ_f, which is the parameter μ in system (3.1).The subscript f is used to emphasis fever state.

$$\mu_f = \mu + \frac{N_0 k\mu(4+3\mu^2)[\delta T T_b + (T_b - T_{en})(T_b + T_{en})]}{(4+9\mu^2)T_b^3(\delta T + T_b)(T_b - T_{en})^2}\delta T \tag{4.14}$$

4.3 Examples

Suppose at healthy state $\mu = 0.5$. Consider daily exercises at healthy state and take fever state when $T_{bf} = 332K, T_{en} = 298K$ as an example. We can compute $div_{\pm}$ to get intuitive picture of how the human body react to perturbation and unhealthy condition. First we can figure out (3.12) and (3.13) at quiescent condition:

$$div_- = -4.68089 \quad div_+ = 0.950251$$

Then the corresponding dE_k and $dE_k + dE_D$ are:

$$dE_k = \frac{kT_b}{\beta} div_+ = 0.950251 \frac{2\kappa\tau}{k\mu\pi}(4+3\mu^2)^{-1}\frac{1}{T_{en}T_b}\frac{(T_b - T_{en})^2}{\Delta r} \tag{4.15}$$

and

$$dE_k + dE_D = -\frac{kT_b}{\beta} div_- = 4.68089 \frac{2\kappa\tau}{k\mu\pi}(4+3\mu^2)^{-1}\frac{1}{T_{en}T_b}\frac{(T_b - T_{en})^2}{\Delta r} \tag{4.16}$$

When daily exercises is added, the (3.12) and (3.13) has a little change, to the order of $O(\epsilon)$:

$$div_- = -4.68089 - 6.62093\epsilon \quad div_+ = 0.950251 - 0.251304\epsilon$$

the corresponding dE_k and $dE_k + dE_D$ are:

$$\begin{aligned} dE_k &= \frac{kT_b}{\beta} div_+ \\ &= (0.950251 - 0.251304\epsilon)\frac{2\kappa\tau}{k\mu\pi}(4+3\mu^2)^{-1}\frac{1}{T_{en}T_b}\frac{(T_b - T_{en})^2}{\Delta r} \end{aligned} \tag{4.17}$$

and

$$\begin{aligned} dE_k + dE_D &= -\frac{kT_b}{\beta} div_- \\ &= (4.68089 + 6.62093\epsilon)\frac{2\kappa\tau}{k\mu\pi}(4+3\mu^2)^{-1}\frac{1}{T_{en}T_b}\frac{(T_b - T_{en})^2}{\Delta r} \end{aligned} \tag{4.18}$$

We can see that the energy absorbtion increases in order to sustain the energy supply for daily exercises while the kinetic energy releases less which means that daily exercises can influence quiescent condition energy metabolism, as ϵ is of higher order and at long time limit it will tend to 0, as a result the system returns to quiescent condition.

Now when human is at fever state, take fever state when $T_{bf} = 332K, T_{en} = 298K$ as an example. The parameter μ changes very slightly:

$$\begin{aligned} \mu_f &= \mu + \frac{N_0 k\mu(4+3\mu^2)[\delta T T_b + (T_b - T_{en})(T_b + T_{en})]}{(4+9\mu^2)T_b^3(\delta T + T_b)(T_b - T_{en})^2}\delta T \\ &= 0.5 + 1.29115 \times 10^{-9} N_0 k \end{aligned} \tag{4.19}$$

Here $k \sim 10^{-23}$, and $N_0 k \geq 10^0$. However this increase of μ does influence the shape or $|div_-| - |div_+|$ of the system. If μ is larger this influence is more explicit. In order to see the influence explicitly, we set $\mu = 0.51$ then:

$$div_- = -4.80586 \quad div_+ = 0.976331$$

the corresponding dE_k and $dE_k + dE_D$ are:

$$\begin{aligned} dE_k &= \frac{kT_b}{\beta} div_+ \\ &= 0.976331 \frac{2\kappa\tau}{k\mu\pi}(4+3\mu^2)^{-1}\frac{1}{T_{en}T_{bf}}\frac{(T_{bf} - T_{en})^2}{\Delta r} \end{aligned} \tag{4.20}$$

and

$$\begin{aligned} dE_k + dE_D &= -\frac{kT_b}{\beta} div_- \\ &= 4.80586 \frac{2\kappa\tau}{k\mu\pi}(4+3\mu^2)^{-1}\frac{1}{T_{en}T_{bf}}\frac{(T_{bf} - T_{en})^2}{\Delta r} \end{aligned} \tag{4.21}$$

The result shows that both energy absorbtion and energy releasing increase which is good for the system to maintain life. If $\frac{\partial \mu}{\partial T_b} < 0$, it means that system (3.1) tends nearer to Hamiltonian system, which implies that the system goes nearer to equilibrium. In Hamiltonian system $div \equiv 0$. And equilibrium for biological system means death, as Prigogine etc have pointed out that nonlinearity and non-equilibrium have close relation [13].

In this section we find the physics behind that intuitive picture: to avoid death, the parameter is regulated to guarantee the system further from the original non-equilibrium state. Of course, the cost is that it does harm to health. Such as the increase of pulse does harm to heart, and it may cause further damage to vessels. Anyway, this regulation drives human body far from equilibrium, that is, far from death. So we have to say that fever is better than death.

5 Conclusion discussion and outlook

(3.1) is the simplest mathematical model of limit cycle oscillation. By phenomenologically establishing the mathematical model (3.1) to describe the human body system, we focus on one of the vital sign: body temperature. In short, fever is the regulation of human body which protects life far from death. Following the logic in this paper, it is easy to conclude that abuse of antipyretics does harm to our health. This conclusion coincides with that in medical science. Our method is helpful to study other symptoms caused by more than one kind of sickness.

Here are some comments on this paper. As human body is quite complex, to some extent the mathematical model (3.1) is too simple. And there are some assumptions seems to be artificial: such as in section 2, the time scale of chemical reaction network and the macroscopic vital signs and in section4, the difference of body temperature and environmental temperature. Our discussion mostly confined in the usual case that environmental temperature is lower than body temperature, while not taking the extreme case into consideration: at south pole or equator.

Anyway, the approach of studying medical science used in this paper provides new aspect. As we have already mentioned in abstract and introduction 1, this approach can be widely used to study other medical phenomena, by starting from symptoms. Simultaneously, this paper provides some approach to study the non-equilibrium physics.

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7 Appendix

7.1 Linearization analysis, dimensional analysis and solution of (3.1)

7.1.1 linearization analysis

Linearize a non-linear system to get its dynamical behavior around its singular point is a routine work. This model has a unique limit cycle around the $(0,0)$ when $\mu > 0$. Linearized part of system (3.1) shows the behavior in the neighbourhood of singular point $(0,0)$:

$$\begin{aligned} tr &= \mu \\ det &= -\omega^2 = 1 \end{aligned} \tag{7.1}$$

In which tr is the trace of linearized part, and det is the determinant of linearized matrix. The eigenvalues of the linearized matrix are:

$$\lambda_{1,2} = \frac{\mu \pm \sqrt{\mu^2 - 4}}{2} \tag{7.2}$$

The real parts of eigenvalues are positive. This result implies that in the manifold in neighborhood of singular point $(0, 0)$ is unstable. Its eigenvectors are exponentially expanding.

7.1.2 Dimensional analysis and solution

Dimensional analysis shows that the system (3.1)'s variables dimensions: $[q_1] = [q_2][t]$ and $[\omega] = [t]^{-1}, [\mu] = [t]^{-1}$. This leads to $[q_2] = [t]^{-1}, [q_1] = [t]^0$. By rescaling, the 2 variables have the same dimension. That is to rewrite (3.1) below such that each equation has the same dimension. i.e. let $\frac{q_2}{\omega}$ be a new variable:

$$\begin{aligned} \dot{q}_1 &= -\omega \frac{q_2}{\omega} \\ \frac{\dot{q}_2}{\omega} &= \omega q_1 + \mu(1 - q_1^2)\frac{q_2}{\omega} \end{aligned} \tag{7.3}$$

and set $\omega = 1$. Anyway the rescaling does not change result.

Readers can consult [26, 27] for the detail of determination of the shape of limit cycle. The first order approximation of limit cycle lies in the equation below:

$$V_0(q_1, q_2) + \mu V_1(q_1, q_2) = [2 - \frac{1}{2}(q_1^2 + q_2^2)]\frac{1}{2}(q_1^2 + q_2^2) + \frac{\mu}{4}q_1 q_2(4 - 5q_1^2 + q_1^4 - 3q_2^2 + q_1^2 q_2^2) = 0 \tag{7.4}$$

the solution of (7.4) approximately gives the shape of limit cycle and its position in phase space. The higher the order we take the more accurate the shape of limit cycle we get. For convenience of calculation, we just take the first order approximation into consideration. The 0-th order shows that the variable q_1 in limit cycle lies in the interval $q_1 \in [-2, 2]$. Readers might immediately notice that the dimension is not right in (7.4). This is just what we want to comment on. To get the 0-th order of Lyapunov function, first find a function which is Hamiltonian like:

$$h = \frac{1}{2}(q_1^2 + q_2^2) \tag{7.5}$$

one immediately discovers that q_1 and q_2 have different dimension. If we continue by using the method provided by [26] to get the 0-th order of Lyapunov function $V_0(q_1, q_2)$ of (3.1) is

$$V_0(q_1, q_2) = [2 - \frac{1}{2}(q_1^2 + q_2^2)]\frac{1}{2}(q_1^2 + q_2^2) \tag{7.6}$$

In fact here we have missed ω. We had better to rewrite (3.1) below such that each equation has the same dimension. i.e. let $\frac{q_2}{\omega}$ be a new variable:

$$
\begin{aligned}
\dot{q}_1 &= -\omega \frac{q_2}{\omega} \\
\frac{\dot{q}_2}{\omega} &= \omega q_1 + \mu(1-q_1^2)\frac{q_2}{\omega}
\end{aligned} \tag{7.7}
$$

So the first order of Lyapunov function is exactly written as:

$$
V_0(q_1, \frac{q_2}{\omega}) = [2 - \frac{1}{2}(q_1^2 + \frac{q_2^2}{\omega^2})]\frac{1}{2}(q_1^2 + \frac{q_2^2}{\omega^2}) \tag{7.8}
$$

As we have already claimed that $\omega = 1$ in previous section, ω is eliminated from the function. And the 2 in $V_0(q_1, q_2)$ also has the dimension $[t]^0$. So the Lyapunov function has the dimension $[t]^0$.

The first order of Lyapunov function is $\mu V_1(q_1, q_2)$. It is immediately get that the dimension of $V_1(q_1, q_2)$ is $[t]$. By the method provided by [26, 27], and take the dimension into consideration:

$$
V_1(q_1, q_2) = V_0(q_1, q_2)\int_0^t ds \frac{\partial[(1-q_1^2)\frac{q_2}{\omega}]}{\partial \frac{q_2}{\omega}} - \frac{\partial V_0(q_1, q_2)}{\partial[\frac{1}{2}(q_1^2 + \frac{q_2^2}{\omega})]}\frac{1}{\omega}\int_0^t ds(1-q_1^2)\frac{q_2}{\omega}\dot{q}_1 \tag{7.9}
$$

This calculation is a bit different from the calculation in [27]. In our calculation, we have taken dimension into consideration, so $\frac{1}{\omega}$ is added in the second integration, in order to keep the 2 terms in the same dimension. After a short calculation, it is easy to get:

$$
V_1(q_1, q_2) = [2 - \frac{1}{2}(q_1^2 + \frac{q_2^2}{\omega^2})]\frac{1}{2}(q_1^2 + \frac{q_2^2}{\omega^2})\int_0^t ds(1-q_1^2) + [2 - (q_1^2 + \frac{q_2^2}{\omega^2})]\int_0^t ds\frac{1}{\omega^2}(1-q_1^2)q_2^2 \tag{7.10}
$$

This result explicitly shows that both of the 2 terms have the dimension $[t]$. As $\omega = 1$ so the terms containing $\frac{q_2}{\omega}$ changes into q_2 and the term containing $\frac{1}{\omega^n}$ in which n is an arbitrary number changes into 1. The forms seems to be unchanged but the dimension is in fact changed.

7.2 Fitting

Numerical experiment shows in table1, we can approximately fit the relation between θ and μ.

7.3 Integrating of $div_\pm$

We can integrate $div_\pm$ as long as θ_1 and θ_2 are figured out. θ_1 and θ_2 are in fact function of the parameter μ. So we just integrate out the indefinite integration, and leave θ_1 and θ_2 determined by 7.2 and 3.1.

μ	solution of (3.8) $\theta \approx \frac{\pi}{3}$	solution of (3.8) $\theta \approx -\frac{\pi}{3}$	solution of (3.9)$\theta \approx \frac{2\pi}{3}$	solution of (3.9)$\theta \approx -\frac{2\pi}{3}$
0	1.0472	-1.0472	2.0944	-2.0944
0.1	0.961558	-1.11144	2.03016	-2.18003
0.2	0.865311	-1.1581	1.98349	-2.27628
0.3	0.779951	-1.19299	1.9486	-2.36164
0.4	0.713189	-1.22008	1.92151	-2.4284
0.5	0.661812	-1.24183	1.89977	-2.47978
0.6	0.621407	-1.25976	1.88183	-2.52019
0.7	0.588751	-1.27488	1.86671	-2.55284
0.8	0.5617	-1.28786	1.85373	-2.57989
0.9	0.538821	-1.29916	1.84244	-2.60277
1.0	0.519139	-1.30911	1.83248	-2.62245

Table 1: Numerical solution of (3.8) and (3.9)

$$\begin{aligned} div_+ &= 2\{\int_0^{\theta_1} d\theta\mu[1-(2-8\mu\cos\theta\sin^3\theta)^2\cos^2\theta] \\ &\quad + \int_{\theta_2}^{\pi} d\theta\mu[1-(2-8\mu\cos\theta\sin^3\theta)^2\cos^2\theta]\} \\ &= 2\mu\{-\theta_1 - \frac{3\mu^2\theta_1}{4} - \frac{3\mu\cos 2\theta_1}{2} + \frac{\mu\cos 6\theta_1}{6} - \sin 2\theta_1 + \frac{\mu^2\sin 2\theta_1}{8} + \frac{\mu^2\sin 4\theta_1}{4} \\ &\quad -\frac{\mu^2\sin 6\theta_1}{16} - \frac{\mu^2\sin 8\theta_1}{32} + \frac{\mu^2\sin 10\theta_1}{80} + \frac{4\mu}{3} \\ &\quad -\frac{16\mu+3(4+3\mu^2)\pi}{12} + \theta_2 + \frac{3\mu^2\theta_2}{4} + \frac{3\mu\cos 2\theta_2}{2} - \frac{\mu\cos 6\theta_2}{6} + \sin 2\theta_2 \\ &\quad -\frac{\mu^2\sin 2\theta_2}{8} - \frac{\mu^2\sin 4\theta_2}{4} + \frac{\mu^2\sin 6\theta_2}{16} + \frac{\mu^2\sin 8\theta_2}{32} - \frac{\mu^2\sin 10\theta_2}{80}\} \end{aligned} \tag{7.11}$$

and

$$\begin{aligned} div_- &= 2\int_{\theta_1}^{\theta_2} d\theta\mu[1-(2-8\mu\cos\theta\sin^3\theta)^2\cos^2\theta] \\ &= 2\mu\{-\theta - \frac{3\mu^2\theta}{4} - \frac{3\mu\cos 2\theta}{2} + \frac{\mu\cos 6\theta}{6} - \sin 2\theta + \frac{\mu^2\sin 2\theta}{8} + \frac{\mu^2\sin 4\theta}{4} \\ &\quad -\frac{\mu^2\sin 6\theta}{16} - \frac{\mu^2\sin 8\theta}{32} + \frac{\mu^2\sin 10\theta}{80}\}|_{\theta_1}^{\theta_2} \end{aligned} \tag{7.12}$$

7.4 Characteristic multiplier of (3.1)

Limit cycle is a stable periodic solution of (3.1). Its stability is related to the property of Floquet multipliers [25, 30]. They are relevant to the time integration of the divergence in (3.2) over a period on limit cycle [30]. Choose arbitrary point (q_{1o}, q_{2o}) on limit cycle. The characteristic multipliers Λ_1, Λ_2 are given by *div* in (3.2):

$$\Lambda_1 = \frac{\Lambda_1+\Lambda_2}{2} + \sqrt{\frac{(\Lambda_1+\Lambda_2)^2}{4} - \exp[\int_0^\tau div(s)ds]} \quad \Lambda_2 = \frac{\Lambda_1+\Lambda_2}{2} - \sqrt{\frac{(\Lambda_1+\Lambda_2)^2}{4} - \exp[\int_0^\tau div(s)ds]} \tag{7.13}$$

The characteristic multipliers are intrinsic [25, 30], so starting from any points on limit cycle gives the same characteristic multipliers. $\Lambda_1 + \Lambda_2$ is related to the trace of matrix

$$\exp[\int_0^\tau ds \begin{pmatrix} 0 & -1 \\ 1 & \mu(1-q_{1o}^2(s)) \end{pmatrix}] = \exp[\sum_{i=0}^n \begin{pmatrix} 0 & -1 \\ 1 & \mu(1-q_{1o}^2(t_i)) \end{pmatrix}] \tag{7.14}$$

in which $t_{i+1} - t_i = lim_{n\to\infty}\frac{\tau}{n}$. So

$$\begin{aligned} \Lambda_1 + \Lambda_2 &= \exp[\sum_{i=0}^n \frac{\mu(1-q_{1o}^2(t_i))}{2}] \qquad (7.15) \\ &\times\{\exp[-\sum_{i=0}^n \sqrt{-1+\frac{\mu^2(1-q_{1o}^2(t_i))^2}{4}}] + \exp[\sum_{i=0}^n \sqrt{-1+\frac{\mu^2(1-q_{1o}^2(t_i))^2}{4}}]\} \end{aligned}$$

The characteristic multipliers are explicitly given by:

$$\begin{aligned} \Lambda_{1,2} &= \exp[\frac{1}{2}\int_0^\tau div(s)ds] \times (e^{f(div)} + e^{-f(div)}) \qquad (7.16) \\ &\pm\sqrt{-\frac{1}{2}\exp[\int_0^\tau div(s)ds] + \frac{1}{4}\exp[\int_0^\tau div(s)ds] \times (e^{2f(div)} + e^{-2f(div)})} \end{aligned}$$

in which $f(div) = \int_0^\tau ds\sqrt{\frac{1}{4}div^2(s) - 1}$. The stability condition of system (3.1) is $|\Lambda_1| < 1$ and $|\Lambda_2| < 1$, which implies that $\int_0^\tau div(s)ds < 0$.

Integrate (3.2) along the limit cycle, we get the exact information of characteristic multipliers, which needs the explicit solution of limit cycle. In section 3.1 and 7.1 we have already explicitly figured out the explicit solution of limit cycle by solving (7.4). Plug the solution of (7.4) into (3.15) then:

$$\begin{aligned} &\Lambda_{1,2} = \exp[-\frac{1}{4}\mu(4+3\mu^2)\pi] \times (e^{\int_0^\tau ds\sqrt{\frac{1}{4}div^2(s)-1}} + e^{-\int_0^\tau ds\sqrt{\frac{1}{4}div^2(s)-1}}) \qquad (7.17) \\ &\pm\sqrt{-\frac{1}{2}\exp[-\frac{\mu}{2}(4+3\mu^2)\pi] + \frac{1}{4}\exp[-\frac{\mu}{2}(4+3\mu^2)\pi] \times (e^{2\int_0^\tau ds\sqrt{\frac{1}{4}div^2(s)-1}} + e^{-2\int_0^\tau ds\sqrt{\frac{1}{4}div^2(s)-1}})} \end{aligned}$$

μ is the perturbation parameter i.e. $0 < \mu < 1$. Again, with the help of numerical results we compare $\int_0^\tau ds\sqrt{\frac{1}{4}div^2(s) - 1}$ with $div_+ + div_-$ in table2. It is not necessary to compute $div_+ + div_- = -\frac{1}{2}\mu(4+3\mu^2)\pi$ when $\int_0^\tau ds\sqrt{\frac{1}{4}div^2(s) - 1}$ is a pure imaginary number. The result demonstrates that the real parts of characteristic multipliers are less than 1.

μ	$\int_0^\tau ds\sqrt{\frac{1}{4}div^2(s)-1}$	$div_+ + div_- = -\frac{1}{2}\mu(4+3\mu^2)\pi$
0	$2\pi i$	-
0.1	$6.25905i$	-
0.2	$6.17961i$	-
0.3	$6.02149i$	-
0.4	$5.73412i$	-
0.5	$5.17682i$	-
0.6	$0.60166 + 4.18517i$	-4.78779
0.7	$1.73889 + 3.47351i$	-6.01458
0.8	$2.95755 + 3.22425i$	-7.43929
0.9	$4.15364 + 3.05592i$	-9.0902
1.0	$5.39099 + 2.91382i$	$-\frac{7\pi}{2}$

Table 2: Numerical integration of $\int_0^\tau ds\sqrt{\frac{1}{4}div^2(s)-1}$ in order to compare with $div_+ + div_-$

We can conclude that apart from the singular point $(0,0)$, the trajectories of the system starting from any points in the phase space (q_1, q_2), will infinitely approach the limit cycle, as long as the starting points are not on the limit cycle. As the real parts of $\Lambda_{1,2}$ exponentially squeeze the trajectories to limit cycle. Schematic figure is shown in Fig. 2

7.5 The computing details for section 4

Integration of the$|div_-| - |div_+|$ and $div_\pm$ when human is healthy but not at quiescent condition:

$$\begin{aligned}
\frac{dE_D}{dt} &= \frac{2\kappa}{k\mu\pi}(4+3\mu^2)^{-1}\frac{1}{T_{en}T_b}\frac{(T_b-T_{en})^2}{\Delta r}(|div_-|-|div_+|) \\
&= \frac{2\kappa}{k\mu\pi}(4+3\mu^2)^{-1}\frac{1}{T_{en}T_b}\frac{(T_b-T_{en})^2}{\Delta r} \\
&\quad \times(-\mu)\int_0^{2\pi} d\theta \quad \{1-[(2-8\mu\cos\theta\sin^3\theta) \\
&\quad -\epsilon\mu(\sin 2\theta - 2\sin 4\theta - 1) + \epsilon^2\mu(\frac{5}{4}\sin 4\theta - \sin 2\theta) + \epsilon^3\mu(\frac{1}{2}\sin 2\theta + \frac{1}{4}\sin 4\theta)]^2\cos^2\theta\} \\
&= \frac{2\kappa}{k\mu\pi}(4+3\mu^2)^{-1}\frac{1}{T_{en}T_b}\frac{(T_b-T_{en})^2}{\Delta r} \\
&\quad \times[\frac{(4+3\mu^2)\pi}{2} + (4\epsilon\pi + \frac{3}{2}\epsilon\mu^2\pi + \epsilon^2\pi + \frac{9}{8}\epsilon^3\mu^2\pi + \frac{73}{32}\epsilon^4\mu^2\pi + \frac{5}{4}\epsilon^5\mu^2\pi + \frac{7}{32}\epsilon^6\mu^2\pi)]
\end{aligned} \tag{7.18}$$

The details of (4.7)

$$\begin{aligned}
\frac{kT_b}{\beta\tau}|div_-| &= -\frac{2kT_b\mu}{\beta\tau}[\int_0^{\theta_1} d\theta \quad \{1-[(2-8\mu\cos\theta\sin^3\theta) \\
&\quad -\epsilon\mu(\sin 2\theta - 2\sin 4\theta - 1) + \epsilon^2\mu(\frac{5}{4}\sin 4\theta - \sin 2\theta) + \epsilon^3\mu(\frac{1}{2}\sin 2\theta + \frac{1}{4}\sin 4\theta)]^2\cos^2\theta\}
\end{aligned} \tag{7.19}$$

$$+\int_{\theta_2}^{\pi} d\theta \quad \{1-[(2-8\mu\cos\theta\sin^3\theta)$$
$$-\epsilon\mu(\sin 2\theta - 2\sin 4\theta - 1) + \epsilon^2\mu(\frac{5}{4}\sin 4\theta - \sin 2\theta) + \epsilon^3\mu(\frac{1}{2}\sin 2\theta + \frac{1}{4}\sin 4\theta)]^2\cos^2\theta\}]$$

and details of (4.8)

$$\begin{aligned} \frac{dE_k}{dt} &= \frac{kT_b}{\beta\tau}|div_-| - \frac{dE_D}{\tau} \\ &= \frac{2kT_b\mu}{\beta\tau}\int_{\theta_1}^{\theta_2} d\theta \quad \{1-[(2-8\mu\cos\theta\sin^3\theta) \\ &\quad -\epsilon\mu(\sin 2\theta - 2\sin 4\theta - 1) + \epsilon^2\mu(\frac{5}{4}\sin 4\theta - \sin 2\theta) + \epsilon^3\mu(\frac{1}{2}\sin 2\theta + \frac{1}{4}\sin 4\theta)]^2\cos^2\theta\} \end{aligned} \tag{7.20}$$

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