Arnold Tongues in human cardiorespiratory systems

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Arnold tongues are phase-locking regions in parameter space, originally studied in circle-map models of cardiac arrhythmias. They show where a periodic system responds by synchronising to an external stimulus. Clinical studies of resting or anaesthetised patients exhibit synchronisation between heart-beats and respiration. Here we show that these results are successfully modeled by a circle-map, neatly combining the phenomena of respiratory sinus arrhythmia (RSA, where inspiration modulates heart-rate) and cardioventilatory coupling (CVC, where the heart is a pacemaker for respiration). Examination of the Arnold tongues reveals that while RSA can cause synchronisation, the strongest mechanism for synchronisation is CVC, so that the heart is acting as a pacemaker for respiration.

Clinical studies reveal that when we are resting or anaesthetised, our breathing often goes into lock-step with our heart-beats, so that for example we breathe once every three heart-beats, and we begin to inhale a fixed time after the most recent heart-beat. It is already well-known that there are connections between respiration and the control of heart-beats, causing our heart-rate to increase during inspiration and to decrease during expiration. This phenomemon is termed respiratory sinus arrhythmia (RSA), and is considered to be one possible mechanism for causing the observed synchronisation between heart and breathing. An alternative mechanism has been posited, called cardioventilatory coupling (CVC). In models of CVC, a ramping demand for breathing is assumed to be modified by a spike of a given height each time the heart beats, and if the spike takes the demand above a threshold, a new breath is taken and the ramping demand is reset to zero. There has been some interest in physiology literature whether the observed synchronisation is caused by RSA or by the spiking demand mechanism of CVC. Some effort has been expended in conducting experiments where one of these mechanisms is removed, to determine which is responsible for synchronisation. Here we combine both mechanisms in one unified mathematical model for cardiorespiratory systems when resting or anaesthetised, reduce the model to a difference equation called a circle map, and use the properties of this map to deduce that while RSA can cause synchronisation, the dominant mechanism is CVC. In other words, we show that the heart can act as a pacemaker for respiration, and that this is a stronger mechanism for synchronisation than respiratory sinus arrhythmia.

I. INTRODUCTION

The term "Arnold tongues" was coined[1] to describe regions in parameter space where an oscillator was locked onto the phase of an external forcing oscillator. Arnold tongues originally arose in circle-map models of cardiac arrhythmias[2,3], where abnormal rhythms can be associated with competition between two pacemakers, and are an important feature of the behaviour of coupled oscillators.

The complex interrelationship between the human cardiovascular and respiratory systems is a subject of intensive physiological and mathematical research[4-11]. There remains some uncertainty about the origin of the coupling[4,11], whether one oscillator is triggering the other[4], whether RSA is important of not[11], and the role played by the central nervous system (since synchronisation is observed in transplanted hearts, which have no central nervous control). The modelling presented here helps shed some light on these issues.

Under anaesthesia, this interrelationship dominates the system as other inputs to respiratory centres are largely absent, and phase-locking or synchronisation between heart-beats and respiration is commonly observed.[5-7] In these clinical studies, this coupling has been widely explored, with different characteristic patterns categorised as type I, II, III and IV, and with a variety of different phase ratios seen between respiration and heart-beat.

An integrate-and-fire model (illustrated in Fig. 1a) has been successfully used to directly match the clinical data[12]. In this model, a ramping demand for the next inspiration starts from the moment of inspiration, with a cardiac spike superimposed once per heart-beat to model the cardiac influence on respiration. When the combination ramp plus spike reaches a threshold, a new inspiration begins. This mechanism for synchronisation has been termed cardioventilatory coupling[6,7,8,12,13] (CVC). Respiratory sinus arrhythmia (RSA, where the heart-rate is higher during inspiration than during expiration, due to pressure reduction and associated withdrawal of vagal activity) is well-known to be an important interaction between cardiac and respiratory systems. RSA was included[12] by varying the heart-rate, using a separate cardiac integrate-and-fire model, with a threshold that varies linearly with respiration phase (Fig. 1b). That is, in this model respiration modulates heart-rate. There has been some care taken in the past to distinguish between the phenomena of modulation and synchronisation[4]. We here follow Boccaletti et al[14] in acknowledging that rather than considering them as separate phenomena, frequency synchronisation can result from periodic modulation of a parameter (the threshold). We see modulation as a modelling consideration, and synchronisation as a possible consequential model behaviour.

Noise was included in the integrate-and-fire model[12] by varying the heart-rate according to a gaussian distribution. This model has been numerically solved and solution behaviours explored and successfully matched in detail with clinical results, to the extent of mapping out in parameter space the phase-locking regions[12,13] (partly illustrated in Fig. 2b). Of particular interest is the example in Fig. 2a of a patient with a heart-rate reducing

in such a way that a transition from a 1:4 ratio through a 2:7 ratio to a 1:3 ratio is seen[12]. As is discussed later, this has intimate connection with a movement through a classic Farey sequence[3] of adjacent Arnold tongues.

The question of whether the observations of phase synchronisation are due to the effect of the heart on respiration (CVC), or to the effect of respiration on the heart (RSA), has been of considerable clinical interest. When ventilation is artificially paced (removing CVC so that heart-beats cannot influence respiration), RSA is still present but no synchronisation is seen[12]. When hearts are paced or in fibrillation[7] (eliminating RSA but not CVC), coupling is still observed. Hence the clinical evidence is that CVC and not RSA is responsible for the observations of synchronisation. We here present a mathematical model, a circle map, derived from the integrate-and-fire model[12], that neatly combines RSA and CVC. The circle map is faithful to the clinical results, but goes further in that it reveals that synchronisation can result from either mechanism, but that CVC is (in a particular mathematical sense) a stronger mechanism than RSA.

II. A CIRCLE MAP MODEL

We follow here the ideas pioneered by (e.g.) Arnold[2] and Glass[1], and further develop understanding of the interactions between heart and respiration by deriving a circle map from the underlying integrate-and-fire models of respiration and heart-rate. Since we ignore other influences (e.g. conscious control, physical activity) on heart and respiration rate, our model is anticipated to be more suitable for resting or anaesthetised patients. We do not include any random noise effects in our model.

RSA refers to the acceleration of heart-rate observed during inspiration. This is modeled in a simplified manner (as in Galletly and Larsen[12]) by using an integrate-and-fire model, in which there is a linearly increasing function which resets to zero when it reaches a threshold. Modulation is accomplished by taking the threshold to be piecewise linear, dropping by a distance Δ halfway through each respiration cycle as illustrated in Fig. 1b. When the function reaches the threshold, the heart beats and the function is reset to zero. An elementary analysis of this model gives the heart-beat times (θ_i) in the form of a circle map:

$$\theta_{i+1} = g_1(\theta_i) \pmod 1, \quad i=0,1,2,...$$

where g_1 is given by

$$g_1(\theta_i) = \begin{cases} \dfrac{\theta_i + T}{1 + 2\alpha T}, & 0 \le \theta_i < B \\ \dfrac{\theta_i + (1-2\alpha)T}{1 - 2\alpha T}, & B \le \theta_i < 1 - T \\ \dfrac{\theta_i + T - 1}{1 + 2\alpha T}, & 1 - T \le \theta_i \le B + 1 \\ \dfrac{\theta_i + (1-2\alpha)T - 1}{1 - 2\alpha T}, & B + 1 \le \theta_i \le 1 \end{cases} \qquad (1)$$

and $B = 0.5 + (\alpha - 1)T$. Note that the terminology *x (mod 1)* means to restrict *x* to the range [0,1) by subtracting the largest integer less than or equal to *x*, so that the times θ_i are normalised on the respiration period, which is taken to be one without loss of generality. *T* is the period of the heart-beat relative to respiration period, in the absence of RSA (when α=0), and we restrict our attention to the clinically practical ranges $0<T<1$ and $0<\alpha<0.5$. Then g_1 is a piecewise linear circle map of degree one, continuous on the circle and monotone increasing. It is easily seen to be conjugate to (and hence dynamically equivalent to) the "tip maps" extensively studied by Uherka et al[15]. The conjugacy is also a piecewise linear map. Note that orbits of g_1 have well-defined rotation numbers[15] (the average change in θ_i per iteration), so that chaotic behaviour is not possible, despite there being a section of g_1 with slope greater than one – the topological entropy is zero (since our map is "subcritical"[15]).

This RSA circle map, which incorporates the influence of respiration on heart-rate, is now modified to allow the heart-beat to influence inspiration in turn. This effect is modeled by taking the heart to beat at a variable time θ_i as given by the above circle map, and by adding a cardiac spike to a linearly ramping respiration demand curve at each time θ_i as illustrated in Fig. 1a. If the spike raises the demand above the threshold, or the demand curve meets the threshold of its own accord, a new inspiration begins and the respiration phase is reset to zero. θ_i is the time immediately before the spike occurs. Heart-beat times are now given by the modified circle map $\theta_{i+1} = g(\theta_i)$ (mod 1) where

$$g(\theta_i) = \begin{cases} g_1(0), & \theta_i > 1 - A \\ g_1(\theta_i), & \textit{otherwise} \end{cases}$$

where *A* is the cardiac spike amplitude. The circle map *g* depends on three parameters (*A*, *T*, and α), is discontinuous, noninvertible, nondecreasing, and piecewise linear. It looks mostly like the map g_1, being constructed of lines with two different slopes, but with a level section for values of θ_i between 1-*A* and 1, and a typical example is plotted in Fig. 3.

Note that while the underlying ramping demand for inspiration is constant in this model, the actual respiration rate is allowed to vary, due to interaction with heart-rate (CVC), which itself varies due to modulation of the threshold by respiration (RSA). The degree of RSA is measured by the parameter α, which is the relative acceleration of heart-rate during inspiration, and a physiologically reasonable range is 0-0.25 (up to 25% acceleration). We explore the range 0-0.5 in this paper. The parameter A represents the feedback effect of a heart-beat on respiration, via vagal influences, and is a normalised measure of how urgently the beat of the heart encourages a new breath to be taken. A has a physiologically

reasonable range of values from zero to a value less than one. A value of one would give complete 1:1 synchronisation and is somewhat outside the reasonable range.

This extended model captures in a simple formula, a relatively complex mutual interaction between the cardiac and respiratory systems, with other influences excluded, so that this model is expected to apply to sleeping or anaesthetised patients rather than to alert patients. It is a combination of the invertible piecewise linear map g_1 (conjugate to the tip maps of Uherka et al[15]) and the map with a horizontal section originally studied by Arnold[2]., and later by Allen[3] and Torras[16]. It also bears some resemblance to the bounding maps studied by Bub and Glass[17], which have horizontal sections, but which otherwise have slopes everywhere greater than one, whereas our maps have regions with slopes less than one. Furthermore, their maps are non-invertible, and the banded chaos seen in their maps is not a feature of our map g.

Phase locking corresponds to periodic orbits under g, and these are usually characterised by the rotation number, which is the average change in θ_i per iteration. We have numerically determined the rotation number for various parameter values, and some of the resulting phase locking regions are presented in Fig. 4. One colour corresponds to one ratio of heart period to respiration period. The coloured locking regions are called Arnold tongues or sausages, and their order is intimately related to an ordering of the rational numbers called the Farey series[18].

Alternatives to phase locking in circle maps include

1. quasiperiodic behaviour, in which the periods of the heart and respiration are not rationally related but otherwise the solution is quite regular or predictable, and
2. chaotic behaviour or low-dimensional chaos, where the solution is irregular and is unpredictable in the long term.

For our circle map g, the only possible behaviours are phase locking and quasiperiodic orbits. This follows directly from the results of Uherka et al[15], as noted above, which apply to the $A=0$ case, and from the results of Arnold[2,3,18], which apply to the $\Omega=0$ case. Furthermore, for a given set of parameter values, only one behaviour is possible, as the rotation number is known to be unique for these maps.

III. DISCUSSION

The clinical results mentioned above, where a transition from 1:4 locking through 2:7 to 1:3 locking is observed[12] as heart-rate drops, are now clearly interpretable as corresponding to a movement through adjacent Arnold tongues in the direction of increasing T, in our parameter space, or in some planar slice through it. This also follows from the fact that the fractions 1/4, 2/7, 1/3 represent part of a Farey sequence of rationals, which govern the layout[3] of the Arnold tongues. This movement is illustrated in Fig. 2b.

It was also noted in the previous section that clinical work indicates that CVC and not RSA is the cause of synchronisation. We find here that modelling the interactions with circle maps reveals a surprise, and also allows us to make supporting conclusions based directly on the mathematical modelling, as follows:

In the absence of CVC (A=0), any synchronisation between heart and respiration is driven entirely by RSA, and is modeled by the circle map g_1. The surprise is that phase locking is an important feature of g_1, resulting in the Arnold sausages in Fig. 4c. However,

since this map is conjugate to the "tip maps" of Uherka et al[15], quasiperiodic orbits are known to occupy a region of positive measure in the parameter space[15]. Hence, while solutions are quite regular, they are phase locked only for those parameter values that fall inside an Arnold sausage. Parameter values outside Arnold sausages give quasiperiodic behaviour, that is, no synchronisation.

In contrast, when CVC is present and when there is no RSA, the map *g* is the same as that studied by Allen[3], and quasiperiodic orbits occupy a set of measure zero in parameter space[3]. In the absence of RSA, our map *g* is also the same as those studied by Torras[16] when considering entrainment by pacemakers. In that work also, phase locking is shown to occupy all of parameter space except a set of measure zero. That is, at some arbitrary set of parameter values, synchronisation is the typical behaviour of solutions, and the probability of not seeing phase-locking is zero when CVC is present (in the absence of noise).

The physiological implication of our modelling is that RSA can cause synchronisation between heart-beat and respiration, and this is a surprise considering the clinical results. However, RSA is a much weaker mechanism in our model than CVC. It is weaker in the sense that the Arnold tongues occupy less of the parameter space, or that there is a significant measure of parameter values that are not in Arnold tongues, so that phase locking is less likely to be observed for some random choice of parameter values. The weakness of RSA as a locking mechanism is qualitatively illustrated by the relatively small area occupied by the (largest) Arnold tongues in Fig. 4c, compared to Fig. 4b.

Phase locking due to RSA will also be more difficult to observe in the presence of noise (say, added to the underlying heart rate), which will smear the edges of Arnold tongues by effectively changing parameter values at random from beat to beat. As noted by Torras[16], this effect can obscure all but the widest tongues.

IV. CONCLUSION

We have found that the relatively simple map *g* captures the essential features of the interactions between human cardiac and respiratory systems, when those interactions are simplified by anaesthesia, and explains and supports a number of recently reported clinical results on phase locking in these systems. Furthermore, the circle map *g* provides a useful way to compare and contrast the effects of RSA and CVC. While the effect of CVC is here shown to be much stronger than RSA, it is interesting and surprising that RSA can cause phase locking at all, since it is such a gentle modulation mechanism. It is likely that this surprise underlies the distinction some researchers (eg, Schafer *et al*[4]) draw between modulation and synchronisation. We see modulation as a modelling feature, with a heart-beat parameter (the threshold) modulated by respiration, and synchronization as a possible effect. The narrowness of the Arnold Tongues, and the fact that non-synchronized behaviour or quasiperiodic behaviour is a set of positive measure in parameter space, corresponds to the fact that synchronization due solely to RSA may be only rarely observed in the presence of noise.

We believe that further refinements or mathematical extensions of this approach, perhaps incorporating more of the physiology of cardiac and ventilatory control, have the potential to shed much more light on the medical implications of cardioventilatory interactions, by simplifying and helping make sense of complicated interrelationships. Understanding these interactions is fundamental to the understanding and treatment of a variety of human respiratory problems.

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FIGURE CAPTIONS

Figure 1. Integrate-and-fire models. (a) A model[12] for the times of inspiration. When the ramping demand for ventilation, augmented by the cardiac spikes that model the influence of heart-beats on respiration (CVC), reaches the dashed threshold line, a new inspiration is begun, and the demand is reset to zero again. RSA is incorporated by using the integrate-and-fire model illustrated in (b) to determine the timing of the cardiac spikes (θ_i) in (a). In this way, the model combines both RSA and CVC. (b) A model for heart-beat times that includes the effects of RSA. A ramping demand for a heart-beat rises with slope $1/T$ until it meets the dashed threshold line, when the heart beats, and the demand resets to zero. RSA is modeled by lowering the threshold at the half-way point by an amount A so that heart-beats increase in frequency during inspiration, and decrease in frequency during expiration. Time is normalised on respiration period, and the period of heart-beats in the absence of RSA is given by the value of T.

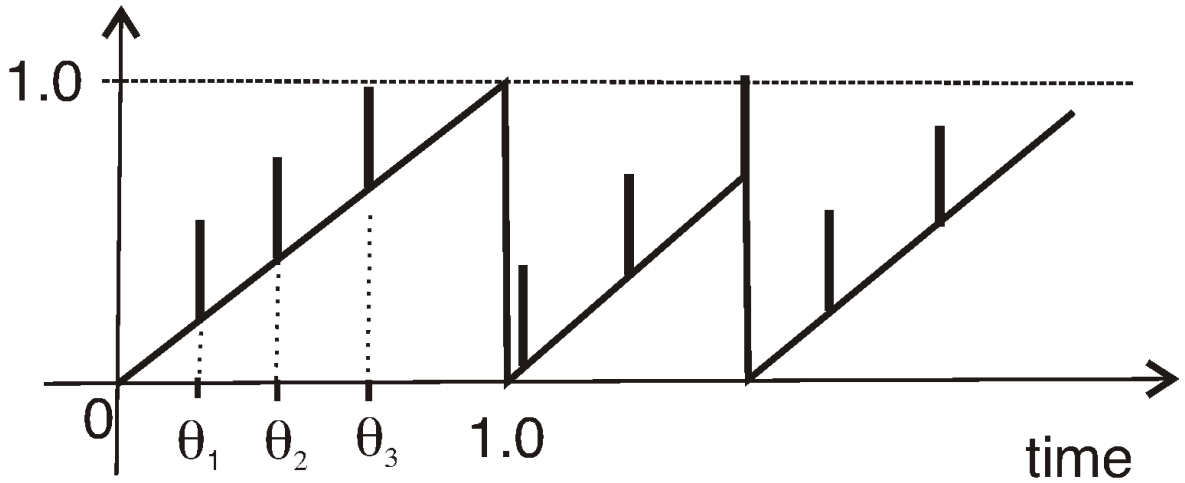
Figure 2. Plots of RI intervals, and phase-locking regions, from Galletly and Larsen[12]. The RI interval is the time in seconds between a heart-beat and the next inspiration, as measured *in vivo*, and in (a) there is a transition from 4:1 locking (in the range 100-250 heart-beats) through 7:2 (in range 250-400 heart-beats) to 3:1 locking. This data was taken at a time when the anaesthetised patient's average heart-rate was decreasing steadily while respiration rate remained relatively steady. In (b) is shown schematically (and rather approximately) a corresponding portion of the phase-locking regions determined by repeatedly numerically solving the integrate-and-fire model of Fig. 1 (a) using an application called LabView[12], and thereby directly determining the phase-locking that is observed for various ratios of heart-rate to underlying respiration rate, and for various values of cardiac spike amplitude A. The heavy arrow that crosses the tongues in (b) is consistent with the sequence of transitions seen in Fig. 2 (a) and with the patient's decreasing heart-rate. RSA was set to zero for these calculations. Note that the horizontal axis corresponds to $1/T$. Also note the similarity of Fig. 2 (b) to Arnold's original plots[2].

Figure 3. The graph of a typical g map. The heavy lines are the graph of g, the dashed lines indicate alignments, and the heavy dashed line is the graph of the diagonal line $\theta_{i+1}=\theta_i$. The function $f(A)$ indicates that the amount of kink in the graph depends on A, with no kink for A zero, and a maximum kink when $A=1$ that causes the elbow to just touch the dashed diagonal line. The kink is exaggerated for clarity, as in practice RSA is rarely higher than 25% ($A \leq 0.25$).

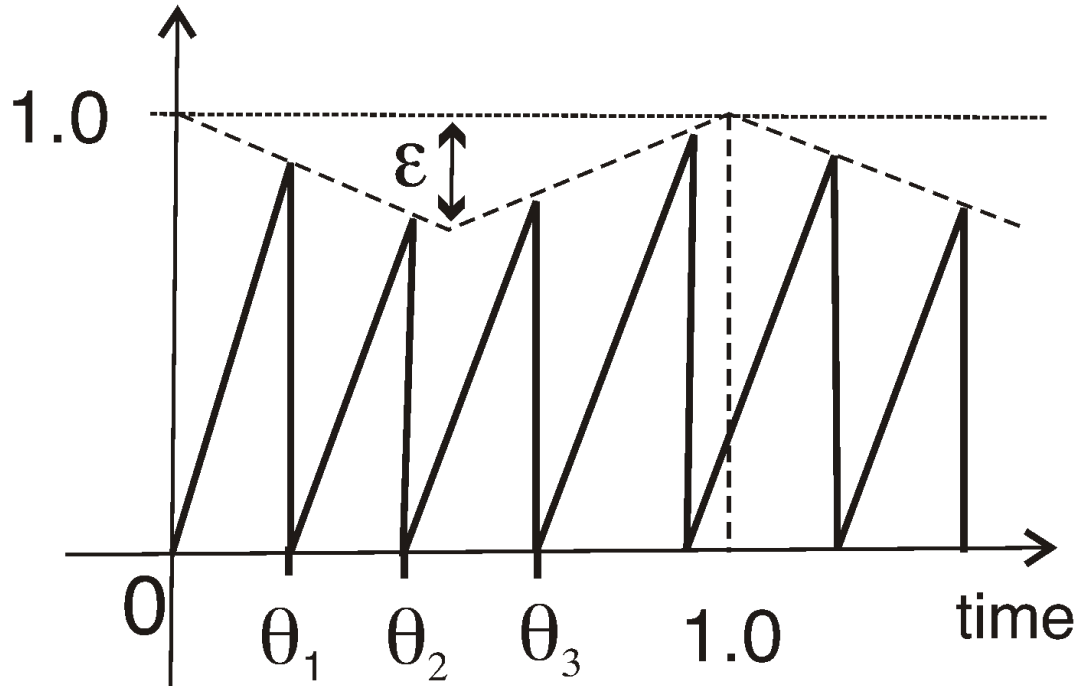
Figure 4. Arnold tongues or sausages for our 3-parameter circle map. We have determined numerically the phase-locking regions up to depth 4 in a Farey series (i.e. for ratios of breathing to heart-rate of 1/5, 1/4, 2/7, 1/3, 3/8, 2/5, 3/7, 1/2, 4/7, 3/5, 5/8, 2/3, 5/7, 3/4, 4/5) and coloured each region. In (a) is a 3D representation of the slices used, which are displayed flat in (b) through (e). The slices with $A=0$ (b) and $A=0$ (c) have been seen before[2,15], and the slices with $A=0.25$ (d) and $A=0.25$ (e) are new, and represent the combined effects of RSA and CVC, but are rather simple modifications or combinations of the previous slices.

McGuinness fig1

a)

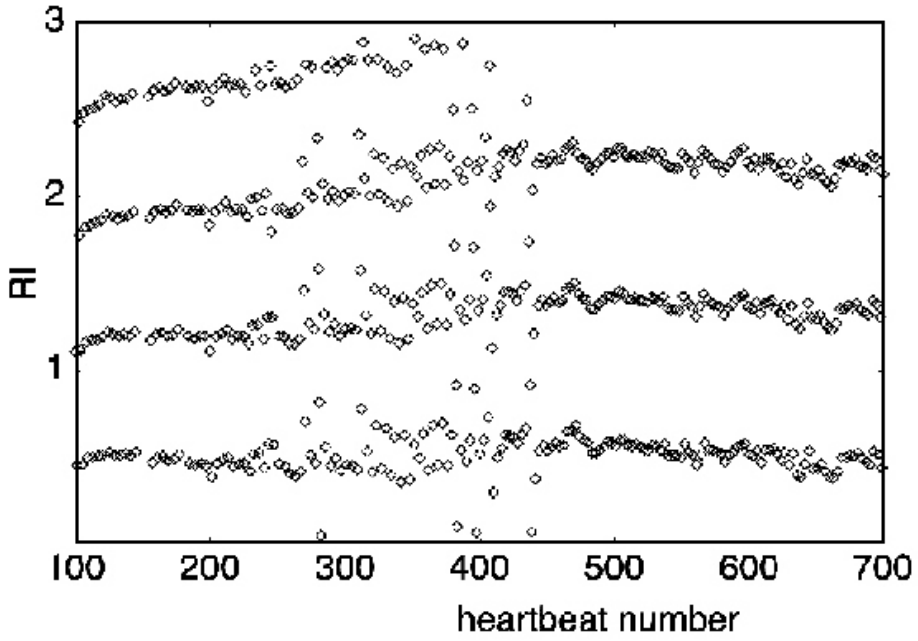


b)

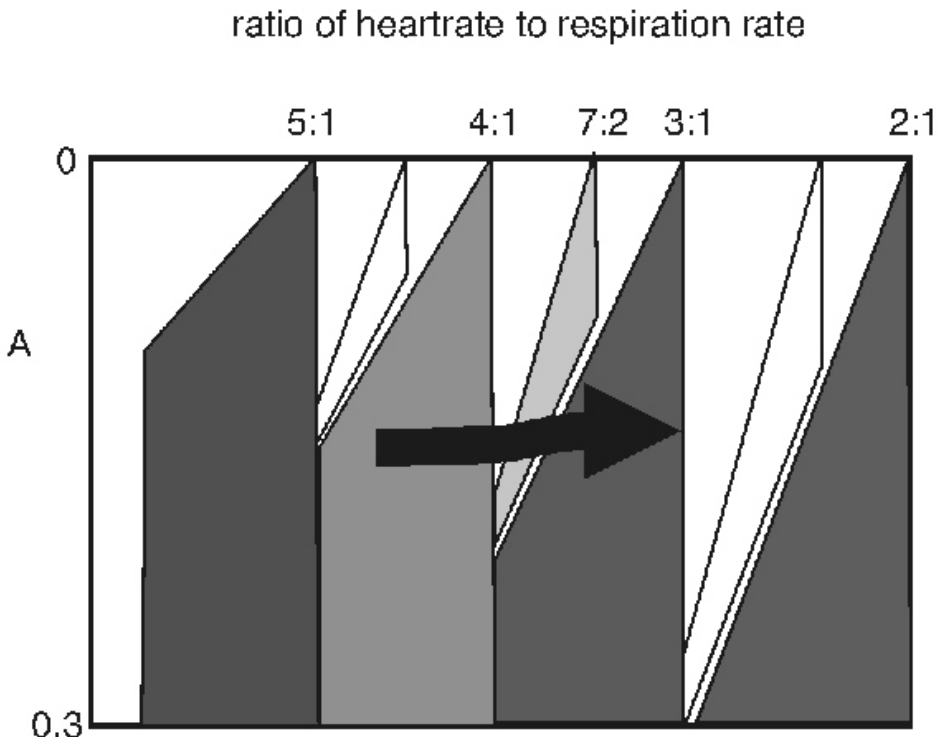


McGuinness fig2

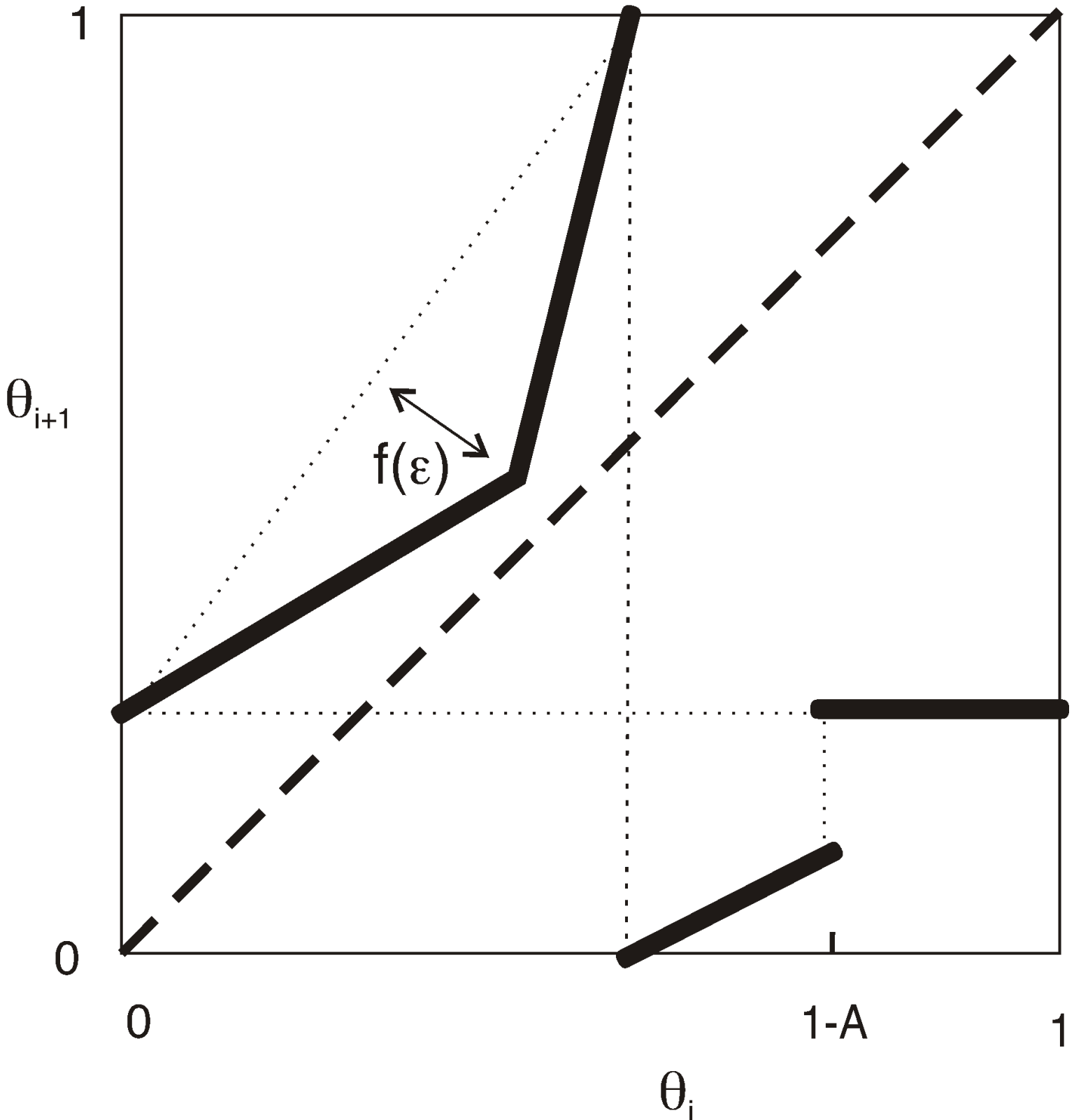
a)



b)



McGuinness fig3



McGuinness fig4