REVIEW PAPER

Thermal sensation and cell adaptability

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Abstract Whole person adaptive comfort is discussed with reference to recent findings in molecular scale systems biology. The observations are upscaled to hypotheses relating to less traditional interpretations of thermal processes, which have new implications for indoor climate management and design. Arguments are presented for a revision of current focus, model and paradigm. The issue is seen as a problem of integrating theoretical development, conceptual modeling and as an investigation of the extent to which environments and acclimatization can be used to achieve individual fitness and health, not only at the subjective comfort level, as hitherto promoted. It is argued that there are many questions yet to be asked about adaptability before celebrating a particular adaptive state.

Keywords Adaptive comfort · ASHRAE standards · Indoor design · Systems biology · Molecular scale adaptation · Cell energy · Shock proteins · Gene expression · Acclimatization · Transduction · Scale integration · Adaptability model

Introduction: adaptive comfort model

This paper explores the "adaptive" comfort model and its relationship to phenotypic (within a life time) adaptation. The issue becomes one of criteria for regulating the mobility of ambient temperature. It goes hand in hand with notions of how to determine and facilitate the attainment of desirable environmental conditions, some of which are yet to be defined;

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others that need re-evaluation. The architecturally oriented reader is invited to regard the present paper as an extension of downloadable material by Auliciems and Szokolay (2007).[1]

The psychophysiological framework of this thermal sensation model is based on Herbert Hensel (1959) and the Auliciems (1981, 1983) biometeorological–techocultural construct "expectancy" as controller. The model provides an alternative of a mobile neutrality to the static solutions of Fanger's (1970) predicted mean vote (PMV). The basis for the model is both theoretical and empirical, not the least being the observation of neutral temperature variability in many field surveys using verbal scales. In these, seasonal differences in comfort sensation had been noted by Yaglou and Miller (1925), Partridge and Maclean (1935), Hikish (1955) and Auliciems (1969, 1972) and Humphreys (1975, 1976).

The so-named "adaptive model" as presented to ASHRAE by de Dear et al. (1997) was the Auliciems (1981, 1983) framework and equation. The American Society of Heating, Refrigerating and Airconditioning Engineers have now finally approved the 55-2004 Standards of thermal environmental conditions for human occupancy, with new amendments that describe adaptive comfort as a valid "model that relates indoor design temperatures or acceptable temperature ranges to outdoor meteorological or climatological parameters". The parameter averaging period, now specified as 1 week or more, is a rational redefinition (unless used as an argument for excluding the use of shorter term meteorotropic attractors).

In brief, the original model justified the use of regression of comfort sensations, as hypothesized in Auliciems (1989, 1972), namely, peoples neutrality shifts in response to pre-

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vailing warmth, or in biometeorological parlance, thermal sensation is meteorotropic. The most commonly observed attractor has been the convenient monthly outdoor mean as in the original equation:

$$T_\psi = 17.6 + 0.31 \ T_{mr} \qquad\qquad (r = 0.88)\ldots \quad (1)$$

where T_ψ is group neutrality and T_{mr} outdoor monthly or running mean temperature as recommended in ANSI/ASHRAE 2010. The significance of the equation and its offshoots is in the regression coefficient 0.31. The algorithm that allows estimation of the thermal indoor-outdoor gradient (or $T_\psi - T_{mr}$) that determines the external energy E_x needed to achieve a mobile or maintain a static PMV neutrality is thus:

$$\%E_x = (T_\psi - T_{PMV})/(T_{PMV} - T_{mr}) \times 100 \qquad (2)$$

Obviously it will be in the most strenuous conditions that adaptation by mobility of neutrality will be of most benefit, but overall most locations (see some annual estimates in Auliciems 1989) benefit from a flexible response as related to the acclimatization possibilities by energy savings between 10 % and 30 %.[2]

Richard de Dear (2011) believes that due to the enabling clauses in ASHRAE Standards (2004) and CEN (2007), more flexible tenets of the benefits of adaptation will prevail in sound economic management approaches and that the final frontier for adaptive thermal comfort researchers will be the "engineering of building occupants' attitudes and expectations". While not altogether in agreement with the accuracy of the historical attributions without historical referencing, the author agrees that the new enabling clauses in ASHRAE Standards may offer a unique opportunity to advance sensation research and its application.

Unfortunately, there has been little effort in development of theoretical context and modeling beyond narrow disciplinary interest. As stated by Andamon et al. (2006), the lack of analysis of cultural factors goes ignored in "adaptive" models. Even after the graphical multilingual scale developments as in Woolard (1981), little had changed in the Anglo-American bias in ASHRAE definition. There has

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[2] For example, the neutrality range in cold climates such that in Riga, Latvia, where average temperature in January is −5 °C and 17 °C in July, and mobile neutrality values are $T_\psi \approx 18$ °C (the minimum acceptable) and $T_\psi \approx 23$ °C. If corresponding values compensated for seasonal clothing and moisture effects as can be estimated from de Dear et al. (1997), PMV is estimated to be≈22 °C and PMV≈25 °C , respectively, the percentage energy savings during a cold spell of say −20 °C would be [18−(22)]/ [22−(−20)]*100, i.e. 4/42 *100≈9 to 10 %, while on average −5 °C E_x would become 4/27≈15 %. In July the gradients on average would not be large enough to justify either cooling or heating on average; a spell of unusually "hot weather" at near 30 °C would modify T_ψ to become≈27 °C for acclimatized people to make the gradient 27−25/25−30= −2/5≈ −40 %, being now biased towards warm discomfort.

been little critical evaluation of linguistic difference in metaphor, cultural preference or experience.

Developments in cognate fields

Building design, microclimate management, ergonomics, exercise physiology and the yet unresolved fundamental question of a definition of optima, seem set to enter a new set of basic postulates. New interpretations of cell energy process and stress seem to provide missing logic and essential solutions, and represent a massive paradigm shift towards the molecular rather than the middle-sized processes of traditional thermophysiology.

During the decades surrounding the 21st century, biological sciences, dealing with molecular scales capitalized on fast developing applications of computer enhanced imagery. Using new technologies of silicon and integrated circuitry, fluorescence and electron microscopy in analysis of biological specimens (see Lewis et al. 1999 for some of the methodology in assessment of cell expression), breakthroughs in understanding of basic life processes appeared in many papers. At the turn of the century, the Singer and Nicholson (1972) cell membrane model had prevailed for three decades, and a vast amount of literature had already appeared on cell structures, shock proteins and energy interaction (Luis et al. 1990).

Many specialist reviews (in cell biology, neuroendocrinology, and genetics) had appeared, but not surprisingly few were specifically interested in speculating about the implications to the whole person. Noteworthy amongst these appeared to be Moseley (1997) on shock proteins (HSP) and acclimatization, and Romanovsky (2007) on neural science and thermoregulatory adaptation. The fields covered are huge and there seems to be little alternative but selective overview.

The genome regulator

Genetic control of thermal response has been the focus of uncountable articles over the past decade. Particularly useful general descriptions and classifications have come from Kregel (2002) and Sonna et al. (2002, 2007). There are now also many specialist monographs available on the thermal response as part of systems biology at the fundamental level (as illustrated for cardiac arrhythmia by Kléber and Rudy 2004, and renal ischaemia and reperfusion injury by Yazihan and Kavas 2010).

The genome defense mechanism to thermal threat is based on more than 120 genes now known to have capacities for adaptation to temperature changes. They have been named, identified by their functional class, chromosome location, species/tissue, in all exposure modes (in vitro, cell culture, whole animal, etc.), timing relative to stage of impact, and

particular mechanisms involved. Continuing mapping of genome controllers appears to provide a strong basis for future scientific integration (O'Malley and Soyer 2011).

Contrary to some persisting misconceptions, the genome is not a fixed repository of information (i.e. an unchangeable intergenerational database). It does provide a blueprint for adaptations within a lifetime that involves longer-term biochemical restructuring, but its response can also be proportional to temporary adjustments to rates of heat loss. Focus on thermal response cycles can individually last only a fraction of a second in cells, and with real-time response capability, the genome is now increasingly recognized not as a passive keeper of evolutionary thresholds but as a dynamic controller of the organism's most sophisticated and at the same time fundamental responses to specific internal and external stimuli of any duration. This capacity for instantaneous response, especially once coupled to energy and electrical potentials in cell transduction, seems to explain some issues in biological control systems, and indeed questions the very notion of a fixed focus homeostatic mechanism as the centre of the whole spectrum of thermal response.

Such a dynamic gene control model also seems to be more commensurate with a sensitive proactive human thermoregulatory system that continuously readjusts energy flows, and adapts through neuroendocrinal sequences, instead of an automated exchange gateway with a passive high entropy store as in Cannon's (1932) homeostasis, and mechanistic energy budget calculations that are unable to switch from the continuous algorithm of regulatory physics to the variable modes of hormonal adaptations.

Increasingly there has been growth of interest in the warning signals themselves that fit into the vast category of neuroendocrinal transmissions that provide the means of communications of information and energy between cells and all genome structures, including individual genes. This would seem to provide a missing link to gene control of the thermal and electrochemical dimensions of human response in general.

TRP neural signals

The sources for cell energy are found in ATP–AD (adinose triphosphate-diphosphate) synthase, active mitochondria (as discussed in Goodsell 1996; Polla et al. 1996; Ban et al. 1999; Gust et al. 2001) and the protein maintained gradients across the critical (Singer and Nicholson 1972) fluid membrane pore permeability (Isenberg and Klaunig 2000; Kléber and Rudy 2004; Phillips et al. 2009; Kimball 2011; Berry and Turberfield 2011). Within the cell energy domain, thermal signals are transmitted from highly receptive and specialized TRP (transient receptor potential) temperature sensors as a series of electrical potential discharges, through

calcium, potassium and other molecular ion channels as pathways to and presumably between individual genes.

The neurobiological significance of the thermosensitive TRP mechanism was described by Caterina et al. (1997, 1999; Caterina 2007; Clapham 2003; Voets et al. 2004; Montell 2005; Patapoutian 2005; Dhaka et al. 2006; Inoue et al. 2006; and Romanovsky 2007).

The TRP channels are about an order of magnitude larger than HSP90, weighing approximately 1000kD. Voets et al. (2004), Dhaka et al. (2006) and most others point to difficulties of explaining the relationship between temperature thresholds and those of electrical discharges, and the functional differences that seem to exist between hot and cold TRP types. Each is separately triggered by their specific threshold signals, as for example, the original TRP1 is sensitive to a 10 °C range about 43 °C (see some critical temperature thresholds in Romanovsky 2007, and voltage discharge derivations by Clapham and Miller 2011).

Temperature–electrical generated events are not evenly or randomly distributed over nerves or organs. The largest concentrations of TRPs are seemingly selectively staged within nerve axons (Montell 2005; Patapoutian 2005; Dhaka et al. 2006). In any case, the lack of homogeneity does not seem to prevent what would appear to be a rapid Hebbean exchange of information (Hebbs 1976), with adjacent thermally sensitive structures (also see Montague et al. 1996). Thus, if HSP72 is the front line defense against thermal threats, the Clapham and Miller (2011) listed "extreme temperature specialists" (high) TRPV1–TRPV4 and (low) TRPA1–TRPM8–TRPC5, may constitute early analysis and communication centres, or advanced signals outposts for upregulating HSP induction and maintenance of storage upkeep.

Clapham's (2003) caption to his review in Nature clearly identified a critical role for the TRP mechanism to thermal sensation as being both the derivative of electrical as well as thermal processes: "TRP channels are the vanguard of our sensory systems, responding to temperature, touch, pain, osmolarity, pheromones, taste and other stimuli. But their role is much broader than classical sensory transduction. They are an ancient sensory apparatus for the cell, not just the multicellular organism, and they have been adapted to respond to all manner of stimuli, from both within and outside the cell."

Not surprisingly, such statements have created exceptional interest in the role of electrical discharges and especially the critical function of calcium ions as a prime trigger mechanism for thermal sensations (Clapham and Miller 2011; Liu et al. 2011; Cheng et al. 2012).

Shock proteins

As observed through computer-enhanced microscopy and a variety of laboratory analyses of biological samples, gene

expression has included shock proteins in structures and functions underlying cell performance and adaptation. Genome expressions of shock proteins in most early reviews, including Burdon (1986), are a response to 'noxious' temperatures. Found in all living cells (Morimoto 1993), heat shock or HSP macromolecules are referred to as being highly conservative, i.e. resistant to evolutionary adaptation. In the present selective overview, however, in as far as possible, items refer directly to humans and phenotypic adaptations, i.e. those within an individual's lifetime.

The cell seemingly supports a routine production of maintenance, constitutional or basal HSPs (Lindquist and Craig 1988; Maloyan et al. 1999) or seemingly smaller conducive types, which are expressed under stress. Mosser et al. (1993) describe HSP as the living cell's first and immediate defense, but one that occurs in responses to many stressors, and with patterns and interactions varied according the HSP family, and species demands. Feder and Hofmann (1999) had tabulated observed correlations between cellular, cellular/organ, organism functions and protein induction. They noted that the magnitude of HSP expression did not correlate well with temperature as such, but did with the induction thresholds for HSP indicating the amount of already achieved adaptation.

HSP are usually divided into six families according to their physical size, ranging from the small <30 kDa to large >100 kDa. Heat was the first recognized of these stressors, hence the bewildering generic singular and plural usage of the acronym HSP and/or HSPs to cover all, including the families of larger sized HSP70 and HSP90, as well as cold shock proteins including HSP38, some of which are also seemingly chaotically labeled by alphanumeric designation (see Sonna et al. 2002).

Unstressed cells appear to also support a resident store of HSP involved in continuous routine repair and essential 'chaperoning' of errant polypeptides away from sensitive fluid membrane pores (see especially Phillips et al. 2009, and Berry and Turberfield 2011). Under mild conditions, thermally strongly oriented HSP70 and HSP90 families are bonded to inactive "monomeric" and HSf transcription controllers (Sonna et al. 2002). Amongst other cell responses to increasing temperature stress, HSP70 (especially HSP72) and HSP90 families are 'recruited' to help new stress 'denatured' proteins, which after fragmentation become disassociated from their HSf companions. This is in concert with other different RNA factors which create new bonding between the cell nucleus and DNA (Shamovsky et al. 2006; Kugel and Goodrich 2006).

HSPs adjustment and adaptation mechanisms appear to vary in diversification of tasks that include folding, assembling and intracellular localization; secretion, regulation, and selective degradation of other proteins seems to be the general universal response to most if not all stressors. As a result of the emergency measures, taken in the resolution of the traumatic protein fragmentation and new induction processes of transcription, splicing and translation, the HSPs achieve an overall stabilization in cell activity and functions. They also carry out repair of structural damage to cell centrosomes and filaments, and the vitally essential maintenance of cell fluidity—and seem to achieve a comprehensive set of programs variously described as structural integrity, cytoprotection, and cell fitness. In all levels, it seems that these functions can be described as endurance and thermotolerance. There is a certain amount of functional overlap between the families, but by far the most active is family HSP70. Broken down by the categories, HSPs can be examined to indicate potential symbiosis in function.

Within the human organism, threats to homeostasis and HSP induction changes can come from many sources: oxygen radicals, heavy metals, ethanol, amino acid and insults (such as hemorrhage and organ malfunction), infection, fever, and inflammation. But the most frequent HSP expression does not require overtaxed organs, excessive thermal stress in clinically recognizable hypothermia or hyperthermia, it results from responses to temperature variability in cellular tissue.

In broad reviews by Javadpour et al. (1998) and Kim et al. (2007), HSP accumulation is typically reported to lead to reversible heat-induced changes in epithelial permeability and to increased general tolerance to endotoxin exposure, and to inhibition of cytokine production by inflammatory cells. The induction of HSPs has been related to reduction of strain and damage to specific cell structures in seemingly most organs including the brain, heart, lungs and kidneys. There has been special interest in the interactions during acclimatization (e.g. leukocytes Yamada et al. 2007; renal performance Yazihan and Kavas 2010). Dokladny et al. (2006) and Horowitz (2007) emphasize that the changes stimulated by enhanced induction of particular proteins during acclimatization leads to cross adaptation and may strengthen resistance in general.

Indeed, there is agreement that HSPs fulfill essential roles within cells, and may become important as either indicators of health, or agents in cross adaptation. Within any of these functions, HSPs become critical items to indoor climate management, and this in itself should promote the realization that some understanding of immunity and adaptations and broad health issues is necessary, and also at least appreciation that human responses cannot be assessed simply in terms of verbalized "comfort" or "preference".

Acclimatization and transduction

Traditionally, acclimatization has been thought of as increased whole person thermophysical response to thermal

stress, but largely as an adjustment to ongoing thermostatic regulatory control and alteration of energy flow rates. On the warm side the transition from adjustment to adaptation is particularly notable in the peaking of sweating, its decreasing effectiveness and alteration of its electrolytic properties. Under cold, there is a rapid increase in thermogenesis, and in both states there is alteration of core temperatures. There appears to be core temperature inflections during STHA "short-term heat acclimatization" (and lesser at the cold STCA). These points probably occur at the maximum stress level, after which the main temperature control by thermophysical exchanges is replaced by neuroendocrinal action that operates with different methods and changed strategies. To what extent and under what circumstances such thresholds are crossed seems to become an important issue for further research.

As suggested by various authors using different analogies and semantics, it seems certain that processes at cellular levels are also those at the larger scale. It is likely that the impacts of signals are mirrored and in general, thermal design has to cater simultaneously for both and interpretations of optima may require different approaches and concepts as at present.

In the healthy, neutrality can be extended by some 1–3 degrees depending upon physical fitness, point of measurement, and other critical factors (Benzinger 1979; Havenith 1997). During this short term (3–5 day) acclimatization there are a variety of physiologically assessable changes (see Armstrong 1998; Sawka et al. 2011; Taylor and Cotter 2006; Moran and Pandolf 1999) that lead to decreased overall stress and elevated performance. Depending upon the episode of noxious thermal signals, the acclimatization symptoms appear to prevail for periods of time variously listed as weeks, months and seasons if not longer, and the process of re-acclimatization is easier after initial exposure (e.g. Nielsen et al. 1993; Garrett et al. 2011).

Given that differences in ion response times, thresholds and action potentials are measurable in fractions of millivolts and milliseconds, it is unlikely that the relatively huge overlaps and differences of natural magnitudes in cycles will ever enable a precise definition of when specific processes can be said to begin, or how much benefit is transferred, but it seems certain that the cell phases are those akin if not directly algorithmically calculable in units of whole body acclimatization. The same model in terms of attenuation rates and relative stress seems to be applicable at the molecular scale, and transduction appears to be the molecular equivalent of whole person acclimatization.

A general similarity in patterns of response of different length acclimatization at both the cellular and whole person scale was noticed by Moseley (1997). Schwimmer et al. (2006) claim that during the shorter-term heat acclimatization, there is a vigorous upregulation of genes responsible for induction of HSP72.

The initial transition from a default thermoregulatory phenotypic condition (such as seasonal neutrality) can trigger transient anti-homeostatic integration and decoding of physical and chemical stimuli blueprints for perception and warning of other potentially harmful events (Maloyan and Horowitz 2002; Collier and Zimbelman 2007).

The earliest linkages of shock proteins as part of acclimatization at the whole person level included those of Nielsen et al. (1993) who noted that during fatigue testing there had been an influx of "plasma" proteins during first exposure to heat, but this molecular scale process was then interpreted only as a side effect of cardiac pressure changes, while endurance was identified as being directly related to seemingly more meaningful core temperature changes occurring during acclimatization.

The recognizable dualism in the continuum of (a) thermoregulatory and (b) neuro-endocrine cascades appeared following publication of the Horowitz et al. model (1996). At the cell level, a follow up to the main HSP overexpression peak is in repair and maintenance of the cell's ability to cope with subsequent stressor signals. McClung et al. (2008) confirmed that in humans there was an elevation in basal HSP induction at least over a 10-day period. But constitutional HSP expression also appears to culminate within hours, following which, according to Maloyan and Horowitz (2002) and Horowitz et al. (2004), volatile thyroid hormones T3 and T4 concentrations decline to 30–40 %. At that stage the body already seems to have at least started switching to a slower and presumably less demanding metabolic hormone regime. This switch seemingly would have been within the latter part of phase ii in Table 1.

While the time taken for HSP expression above basal levels depends on the family to which they belong, on average, accumulation in the intact body seems to be able to appear within minutes following stress exposure, and retain strong activity for a few days. Heat shock proteins seem to appear soon after rises in core temperatures usually assumed to be 37 °C, and cold stress asymmetrically some 5 degrees lower (at approx 32 °C). Basu et al. (2002) suggest a half life of 6–9 h, when at the conclusion of this front line cell defense, the HSf1 protein rebinds to newly synthesized HSP.

In simple terms of amounts and rates of HSP induction in response to general environmental temperature cycles, some physiological periodicities have been reviewed for whole marine organisms and fish (Tomanek and Somero 2002; Basu et al. 2002), and terrestrial poikilotherms (Seebacher and Murray 2007). The significance of such observations however is difficult to assess in terms of human design temperature requirements.

Acclimatization is a broad process that does not necessarily require stress but possibly planned forays into marginal zones by sentient individuals. Indeed the virtually instantaneous expression of the HSPS, the control coordination by the genome and the remarkable logistical placements of TRPs and sequences are not chaotic with respect to time or location, which indicates that sentience exists at the fundamental level.

Table 1 A neo-GAS three phase concept for *Human Thermal Adaptability*

The *avocado* shape aims to portray the progress of the acclimatization process extended for a time period of minutes to weeks through cell transduction to full acclimatization. From the initial upregulation of HSPs within phase I, there is mounting sress and progression from adjustment to adaptation mechanisms cresting at the maximized homeostatic evaporative flux at A (STHA) in 3–5 days. The "breaking crest" of the log-normal aggregated thermal stress is represented by the drift downwards fom the core towards as the ultimate "behavior" stage in phase iii

Operating within some 14–16 °C range of sensation responses of the normal 7-point ASHRAE scale, there seem to be are at least three main phases of thermal response that could be described on an adaptive continuum. i. Adjustment ii Transduction iii Adaptation. Such phases may be seen to be determined by the severity of the thermal stressor and the types of defensive mechanisms available

Table 1 also shows the original zones devised by Hans Selye (e.g. 1936, 1950, 1974), that constituted the General Adaptation Syndrome of GAS, here simplified and labelled as arousal , adaptation and recovery being the main functions of his phases. Selye (1936) also used the term "adaptation energy", or "adaptability" as being the seemingly non-renewable genotypical adaptation energy available

The Transduction label for phase *ii* is used here to give emphasis to the purpose for the categorization being temperature- building design continuum, as opposed to thermo-physiological balance models, Selye's (1936) model used to describe clinical stress management being also a forerunner of many biological works, Cox (1978) sports medicine whole person transactional exercise focus and the allostasis load reduction system of Sterling and Eyer (1981, 1988) and McEwen (1998a, b)
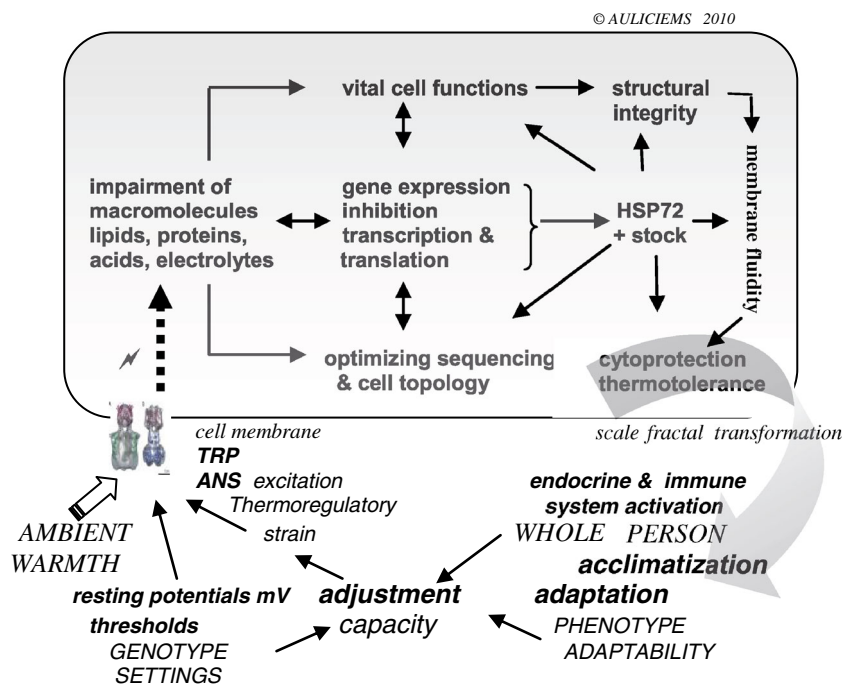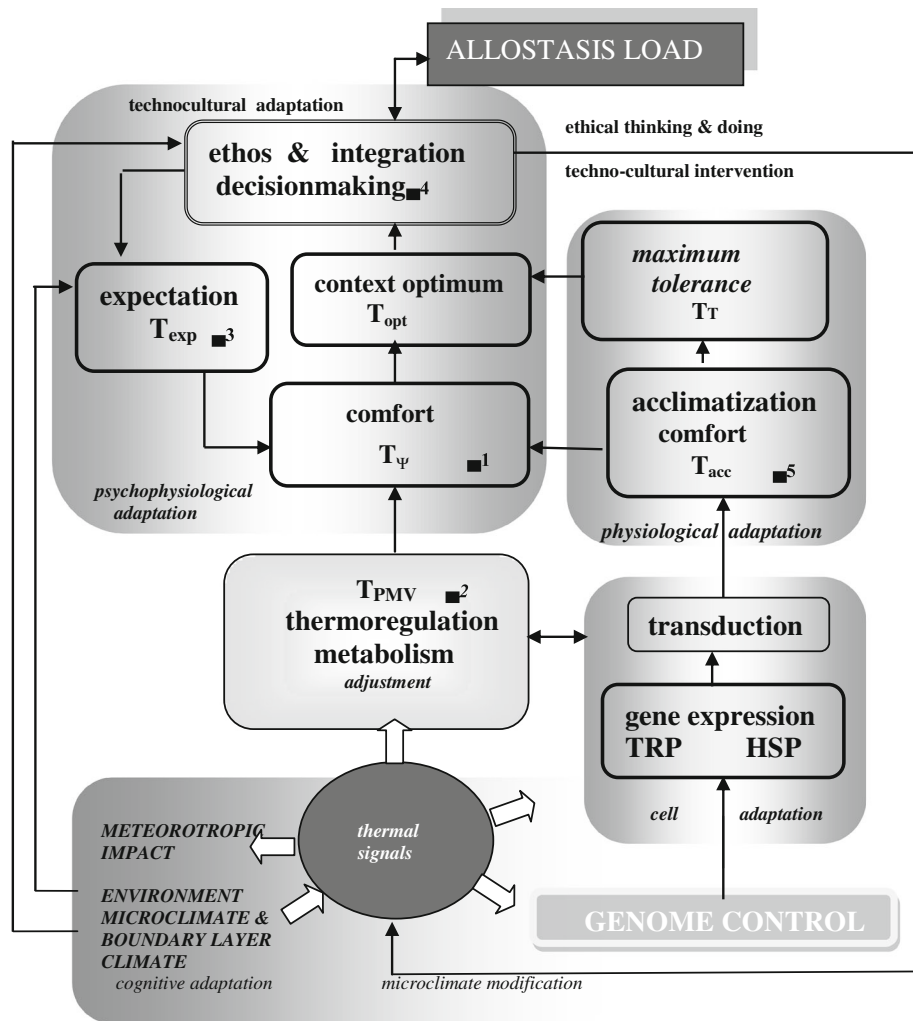

Fig. 1 Hypothetical cell energy transduction cycle (based on Moseley 1997; Clapham 2003; Romanovsky 2007; Digel et al. 2008). Signal↗ *TRP images from* Moiseenkova-Bell et al. (2008). Reconstruction of TRPV1ion channel atomic structure and a Kv1.2 potassium channel as revealed by electron cryomicroscopy are used for notional illustration

Fig. 2 A framework model of thermal adaptability suggested replacement for "adaptive comfort"

Digel et al. (2008) regard TRP channel signals as being the most sensitive of communications, "…at the forefront of our sensory stem." To assist visualization of such a multi-scaled and continuous process, Fig. 1 is offered as illustration for basic cell transduction.

An adaptability model

The cost of crossing the boundaries between adjustment and adaptation is complicated, and will depend upon the degree of exposure to stress, and the tolerance, that is, the physical fitness of the individual. The implications to indoor climate management are no longer a question of defining adjustment, neutrality, sensation or preference, and then designating arbitrarily simple 'comfort' temperatures. It would seem that the new systems biology findings both support and reject the adaptive comfort model. In general the induction of HSP identifies a basic adaptive process at all scales and measurement may become possible of direct translation to both cell stress and integrated sensation. HSP may enable improved classification of atmospheric data in terms of direct indices of strain, and enable better prediction of neutralities and necessary thermal adjustment than semantic scales.

There needs to be analysis that involves determination of what is the context, and what is meant by any optimum. Obviously comfort statements should not be ones of simple ambient measure for a particular activity, or one amount of necessary adjustment defined by overgeneralized linear equations. Perhaps most significantly there may be a need to radically review the designer's responsibility and basic understanding of the relative merits of achieving comfort, while also ensuring that there is adequate opportunity to encounter stimulating temperatures beyond the comfort zone. In the case of enhancing acclimatization, the general solution would be in maximizing an overall drift towards adaptation, i.e. from adjustment phase i categories towards phase iii in Table 1, without violating pre-established individual health requirements.

Until a more comprehensive design is produced, Fig. 2 based on the above overview is offered as an alternative to the now defunct 1981 adaptive framework. The substantial difference is in differentiating between adjustment and adaptation as understood within GAS, the former being a transient change in response intensity, the latter being persisting bio-chemical alteration. It is useful to also consider two independent controllers, being genetic for biological short-term cellular and whole body acclimatization, and decision making for the main contextual expectation. Further, division can be made between cell, thermoregulatory–physiological and psychological and technological levels. Thermal stress and the traditional ANS and CNS are modified by both long- and short-term feedbacks from adjustments and adaptations.

Gene control at the level of cellular molecular processes operates in expressions of TRP and HSP, as part of cytological protection, increased thermotolerance and energy transduction at the beginning of the acclimatization and biological adaptation at the whole person scale. Promotion of exercise and fitness through design and microclimate modification provides massive negative feedback from psychological adaptations that provide the necessary external control through the cognitive modules of decision-making and expectation.

To provide for inclusion of these complexities, in Fig. 2 the normal environmentally driven variable neutrality (T_Ψ), being the measured naturally occurring seasonal acclimatization neutrality value (at present the context specific adaptive model prediction using monthly mean temperature for a location), is supplemented in T_{opt} by T_{Tmax} the increment by short-term acclimatization. Should there be good reason to reject seasonality as a factor (i.e. as may be the case of the medium-term itinerant soldier or athlete, or even the otherwise fit but habitually air-conditioned traveler), there may be reason to use Fanger's T_{PMV} in lieu of T_Ψ.

In looking at a future integration with other priorities, the ethos module would be joined by inputs from other allostatic systems.

Whatever the context, full acclimatization during warm and cold episodes will incur increased and seemingly upgraded neuroendocrinal adaptations, and less thermal adjustments. This adaptation will allow increased thermal tolerance and tempering in one sector, but also produce strain in other dimensions, at a cost to Selye's adaptation energy. Thus in any recommendation or design some safety margin needs to be identified—the critical edge between net benefits of adaptation over its costs. It is suggested that this boundary is represented less as the onset of active sweating, but as maximum time in particular environments that can be enjoyed by acclimatized individuals. While not entirely symmetrical, active thermogenesis in cold should be encouraged, and until the easy availability of molecular thermometry or validation of some HSP expression can be used as an index, adaptation (acclimatization) plateaux should be used as basic criteria for recommendations.

Conclusion

Genome 'expressed' heat shock proteins in particular, seem to overcome what may have been to some an impossible conceptual obstacle of size difference. If combined, TRP and HSP expression, plus genome capacity for instantaneous response seems to explain some bewildering issues in biological control systems, and indeed questions the notion of a fixed focus homeostatic mechanism as the centre of the whole spectrum of thermal response. Building design, microclimate management, ergonomics, exercise physiology and the yet unresolved

fundamental questions of a definition of optima seem to enter a new set of basic postulates, which may require new interpretations of adaptability and time as episodic acclimatization processes.

At this stage of development in the new systems biology, and until the full potential of expressions of HSPs as indicators of adjustment and/or adaptation, and most suitable biological thermometers are assessed, any conclusions are likely to be interim solutions at best. However, with reference to the adaptive model, for the time being there are good economic and health reasons to continue promotion of variability in neutrality, but avoid emphasis upon vague principles of comfort, comfort zones or specification of precise thresholds. The merits of fitness and encouragement of exposure to stimulating environments should underlie all programs of planned activity and design. The opportunities for improved application and education as suggested by de Dear (2011) are probably valid, but to do so, there is argument for improving scholarship and adhering to scientifically testable models that have appropriate capacities for assessment of human requirements.

The Basu et al. (2002) argument is that a fundamental issue for research in genomics and physiology is to resolve the relationship of cellular stress to organismal stress and optimum responses (including adaptation limits) at the higher level processes. To Hood et al. (2004) it would also seem that the new paradigm must be a sentient one that recognizes that molecular systems are close to explanation of many of the fundamental mechanisms, including thermoregulation and adaptation. To them the new concepts are transforming current diagnostic and therapeutic approaches towards 'personalized medicine'. Such a move away from statistical generalization towards optimization of an individual's 'private climate', as based on a paradigm of deeper analysis and wider scholarship, would not be unwelcome to systems biology, architectural or biometeorological integration.

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