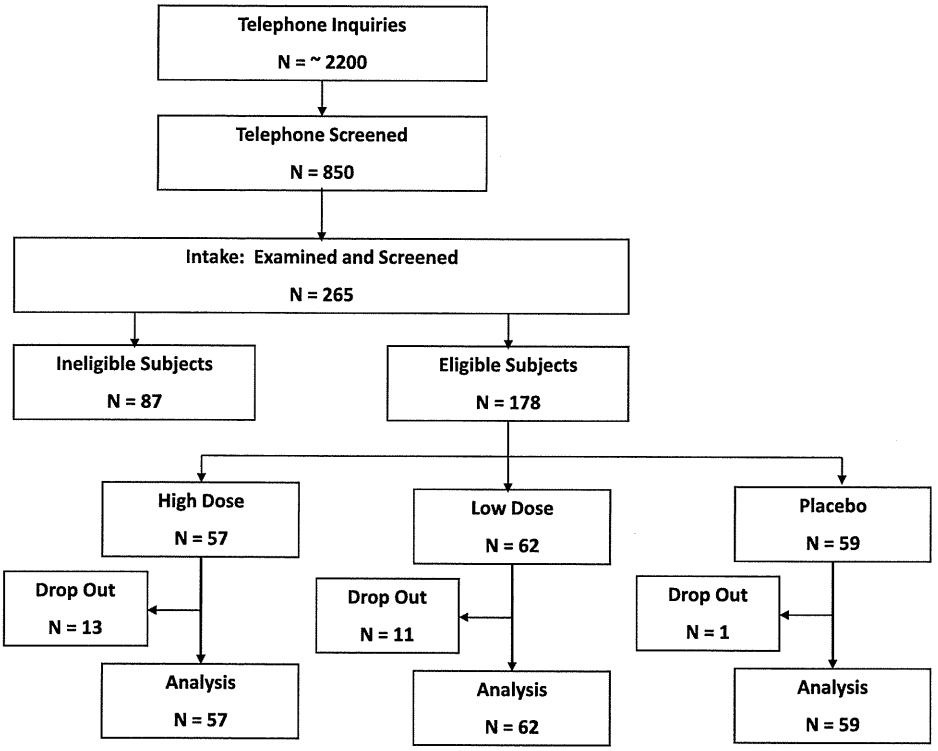


FIG. 1. Disposition of study participants.

Measures

The study included three primary efficacy variables: (1) the frequency and severity of hot flash symptoms, (2) climacteric symptoms, and (3) sleep quality. The daily Mayo Hot Flash Symptom Diary was used for determining the frequency and severity of hot flashes.[22,24] The daily diary was brought at each monthly visit. The score was aggregated and summarized as a daily average number of hot flashes and hot flash scored based on frequency and severity. Climacteric or menopausal symptoms were summarized using the GCI.[25,26] Sleep quality was assessed using the PSQI.[27,28] For the eight PSQI scales, the overall sleep quality and overall indices were treated as the primary outcomes. The GCI and PSQI questionnaires were completed in clinic at baseline and at 1, 2, and 3 months after enrollment. Adherence was evaluated by pill counts at each visit. Liver function tests and complete blood counts were obtained at each visit. Hormone measurements were obtained before enrollment and at the end of participation. After the last woman completed the study, all participants were contacted by telephone and asked to guess their treatment group assignment.

TABLE 1. *Demographic characteristics of women enrolled in the TU-025 hot flash management study*

	Placebo (n = 59)	Low dose (n = 62)	High dose (n = 57)	Total (n = 178)
Age[a], y	53.3 ± 0.38	53.7 ± 0.38	53.6 ± 0.49	53.3 ± 0.24
White race[b]	57 (95.0)	58 (93.6)	54 (93.1)	169 (93.9)
Marital status[b]				
Married	47 (78.3)	47 (75.8)	41 (70.7)	135 (75.0)
Divorced	6 (10.0)	10 (16.1)	10 (17.2)	26 (14.4)
Widowed	0 (0.0)	0 (0.0)	2 (3.5)	2 (1.1)
Separated	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.6)
Never married	4 (6.7)	2 (3.2)	2 (3.5)	8 (4.4)
Member unmarried couple	2 (3.3)	3 (4.8)	3 (5.2)	8 (4.4)
Level of formal education[b]				
High school graduate	4 (6.7)	10 (16.1)	4 (6.9)	18 (10.0)
Some college or technical	19 (31.7)	20 (32.3)	21 (36.2)	60 (33.3)
College graduate	37 (61.7)	32 (51.6)	33 (56.9)	102 (56.7)

[a]Values are expressed as mean ± SEM.
[b]Values are expressed as n (%).

RESULTS

From the 265 women seen at intake and evaluated for inclusion in the study, the final study included 178 eligible women. (Fig. 1) Eighty-seven individuals were excluded because of the following reasons in order of frequency: (1) a

TABLE 2. *Baseline menopausal history for women enrolled in the TU-025 hot flash management study*

History of menopause	Placebo (n = 59)	Low dose (n = 62)	High dose (n = 57)	Total (n = 178)
Natural menopause	46 (78.0)	50 (80.7)	44 (77.2)	140 (78.7)
Hysterectomy without oophorectomy	4 (6.8)	5 (8.1)	8 (8.8)	14 (7.9)
Partial oophorectomy	0 (0.0)	1 (1.6)	1 (1.8)	2 (1.1)
Oophorectomy	9 (15.3)	6 (9.7)	7 (12.3)	22 (12.4)

Values are expressed as n (%).

TABLE 3. *Physical findings at baseline for women enrolled in the TU-025 hot flash management study*

	Placebo (n = 59)	Low dose (n = 62)	High dose (n = 57)	Total (n = 178)
Anthropometric measures[a]				
Height at intake, cm	165.6 ± 0.8	163.9 ± 0.9	53.6 ± 0.5	165.3 ± 0.8
Weight at intake, kg	71.3 ± 1.5	70.9 ± 1.8	53.6 ± 0.5	71.5 ± 1.7
Body mass index, kg/m^2	26.0 ± 0.5	26.3 ± 0.6	53.6 ± 0.5	26.2 ± 0.6
Obesity classification[b]				
Underweight (<18.5 kg/m^2)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.6)
Normal weight (18.5-24.9 kg/m^2)	25 (42.4)	25 (40.3)	27 (47.4)	77 (43.3)
Overweight (25.0-29.9 kg/m^2)	26 (44.1)	22 (35.5)	18 (31.6)	66 (37.1)
Obesity class I (30.0-34.9 kg/m^2)	5 (8.5)	11 (17.7)	8 (14.0)	24 (13.5)
Obesity class II (35.0-<36 kg/m^2 in this study)	3 (4.8)	3 (4.8)	4 (7.0)	10 (5.6)
Blood pressure, mm Hg[a]				
Systolic blood pressure	123.6 ± 1.9	126.1 ± 2.0	53.6 ± 0.5	124.2 ± 1.8
Diastolic blood pressure	72.0 ± 1.1	71.3 ± 1.2	53.6 ± 0.5	70.7 ± 1.2
Pulse rate, beats/min[a]	71.9 ± 1.4	69.3 ± 1.5	53.6 ± 0.5	71.9 ± 1.7

[a]Values are expressed as mean ± SEM.
[b]Values are expressed as n (%).

Beck Depression Inventory score of more than 11 (24/87); (2) an insufficient number of baseline hot flashes (20/87); (3) laboratory values being out of range (15/87); (4) not being in menopause (7/87); and (5) a BMI greater than 36 kg/m^2 (5/87).

Table 1 shows the demographic characteristics of the women enrolled. Participants were nearly evenly divided between the three groups. The groups were comparable with one another in terms of age, racial status, marital status, and educational level. None of the observed differences in characteristics was statistically significant across the study groups. On average, the women enrolled were in their early 50s (age, 53.6 y), white, married, and well educated.

Approximately 80% of the women experienced natural menopause (Table 2). Based on medical histories obtained, one in nine of the women (12.4%) had had a bilateral oophorectomy. There were no statistically significant differences between the groups in terms of their medical history.

Table 3 shows the core physical findings for these women at baseline. Overall, most of the women enrolled were either slightly overweight or obese. The mean BMI for these women was 26.1 kg/m^2. Between the intervention conditions, there were no statistically significant differences in these core physical findings at the time of intake.

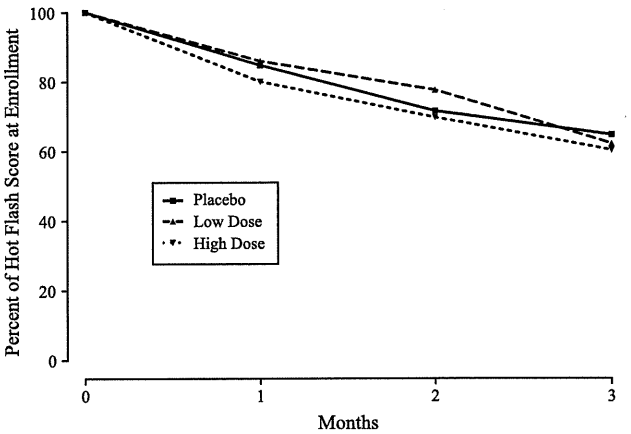
Baseline estradiol and FSH levels are shown in Table 4. No statistically significant differences exist between the intervention conditions. Approximately three in five women were found to have estradiol levels less than 21 pg/mL, and three in four women had FSH levels greater than or equal to 60 mIU/mL. These levels are consistent with those found among women at menopause.

TABLE 4. *Baseline hormone levels for women enrolled in the TU-025 hot flash management study*

	Placebo (n = 59)	Low dose (n = 62)	High dose (n = 57)	Total (n = 178)
Estradiol levels, pg/mL	22.9 ± 1.8	20.6 ± 2.2	21.4 ± 1.9	21.6 ± 1.2
≤20	34 (57.6)	39 (62.9)	34 (59.7)	107 (60.1)
21-50	21 (35.6)	22 (35.5)	21 (35.6)	64 (36.0)
≥50	4 (6.8)	1 (1.2)	2 (3.5)	7 (3.9)
Follicle-stimulating hormone levels, mIU/mL	81.5 ± 3.5	79.1 ± 3.2	79.5 ± 3.2	80.0 ± 1.9
≤39	1 (1.7)	2 (3.2)	1 (1.8)	4 (2.3)
40-60	12 (20.3)	14 (22.6)	11 (19.6)	37 (20.9)
≥60	46 (78.0)	46 (74.2)	44 (78.6)	136 (76.8)

Figures 2 and 3 summarize the mean hot flash diary scores at baseline and at 1, 2, and 3 months. Figure 2 depicts the change and percentage change in the average monthly hot flash scores. Figure 3 depicts the change and percentage change in the numbers of hot flashes at monthly visits. At 3 months, the results from the hot flash scores showed a decrease in all three groups: 34% in the placebo group, 40% in the 7.5 g/day group, and 38% in the 12.5 g/day group. Although these declines in mean scores were significant ($P < 0.001$) within each group, the differences between groups were not statistically significant ($P = 0.990$).

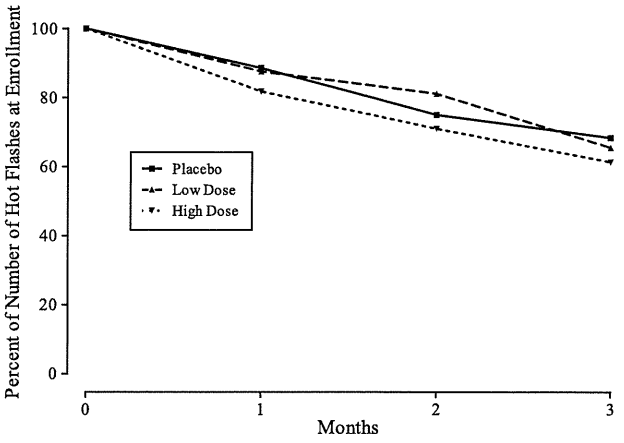
The mean scores for the GCI, which includes Depression, Anxiety, Psychosocial, Somatic, Vasomotor, and Sexual



Test for Fixed Effects

	Num DF	Den DF	F Value	P value
Treatment Group	2	172	0.27	0.765
Month	3	516	56.09	< 0.001
Month * Treatment Group	6	516	0.38	0.892

FIG. 2. Percentage of hot flash score at enrollment according to treatment group and month after enrollment. DF, degree of freedom.



Test for Fixed Effects

	Num DF	Den DF	F Value	P value
Treatment Group	2	172	0.84	0.434
Month	3	516	65.53	<0.001
Month * Treatment Group	6	516	0.71	0.640

FIG. 3. Percentage of number of hot flashes at enrollment according to treatment and month after enrollment. DF, degree of freedom.

Dysfunction Indexes, declined significantly across the study (all P values < 0.001). However, no statistically significant treatment group by month interaction was observed.

The PSQI and its associated subscales demonstrated a statistically significant attenuation in all scores for all the participants across the study (all P values < 0.001), except for sleep medication use, which remained constant across the study. The Beck Depression Inventory summarized at intake and conclusion demonstrated some improvement in mood ($P = 0.044$), with no significant differences between treatment groups (data not shown).

Twenty-five women (14.0%) withdrew before completing the 12-week study. There were no statistically significant differences in the likelihoods of withdrawing across the treatment conditions ($\chi^2 = 4.12$; $df = 2$; $P = 0.127$). The primary reason for withdrawal was diarrhea (15/25) followed by persistent hot flashes (6/25). Diarrhea was present in approximately 20% of the participants receiving active medication (Table 5). This diarrhea was statistically significantly more prevalent in the low-dose and high-dose groups compared with the placebo group ($\chi^2 = 12.05$; $df = 2$; $P = 0.002$).

DISCUSSION

Despite supportive animal model data in peer-reviewed literature as well as the widespread use of prescription TJ-25 in Japan for perimenopausal women, this rigorous randomized controlled trial failed to demonstrate the efficacy of TU-025 beyond placebo for reducing the severity and frequency of hot flash symptoms, climacteric symptoms, or disrupted sleep symptoms in postmenopausal American women. Failure to find a treatment benefit was unlikely to be related to breaches in study protocol, participant adherence, statistical power, and length of follow-up.

Despite the use of a 1-week placebo lead-in period to minimize the enrollment of placebo responders and despite the additional 12 weeks of study duration, clinically significant reductions in hot flash severity and frequency were experienced in a significant portion of the women receiving placebo. The 34% rate of placebo response is consistent with that reported in other clinical trials. However, the placebo effect was expected to resolve before 12 weeks of therapy. Future herbal medicine trials should measure participant expectations at the time of enrollment. In this study, several participants noted afterward that they enrolled to "prove" that herbal medicines work. This suggests the presence of a significant *meaning* response.[29]

Unlike the study of a single Western herb with candidate marker ingredients for monitoring serum levels, the translation of a unique healing system, such as Kampo diagnoses and therapeutics, into a Western model is faced with limitations that may have not been appreciated. Despite the strengths of the study, three methodological concerns are important to recognize for future trials of a products taken out of their whole-system context.

The first concern is the selection of the study population. Following the FDA guidelines, we restricted the entrance into this study to women who had experience cessation of menses for more than 1 year. This meant that many women who requested enrollment were excluded. Traditional Kampo practitioners do not include a women's menstrual status in formula decisions. In addition, women with depressed mood as determined by Beck Depression Inventory scores (>11) were excluded from the study and requested to work with a physician regarding the possibility of depression. The reasoning was that women at risk for significant depression should not be enrolled when proven effective antidepressant therapy that also addressed hot flashes was already available. We did not realize that nearly 100% of these women refused to consider the prescription of antidepressant therapy and attributed their depressive symptoms to severe life disruption by hot flashes/night sweats. Exclusions because of menopause status or an elevated depression score may have introduced bias in enrollment.

Second, inclusion criteria did not consider the traditional Kampo assessments of each participant's *sho* or constitutional state. Although completely contrary to Kampo practice, every woman who met the FDA entrance criteria was enrolled into the study. Per Kampo tradition, keishibukuryogan is best

TABLE 5. *Prevalence of unanticipated diarrhea (adverse event) among the 178 women enrolled in the hot flash study*

Frequency	Placebo (n = 59)	Low dose (n = 62)	High dose (n = 57)	Total (n = 178)
No, n (%)	58 (98.3)	48 (77.4)	46 (80.7)	152 (85.4)
Yes, n (%)	1 (1.7)	14 (22.6)	11 (19.3)	26 (14.6)

matched to women with *hiesho* (subjective coldness) and *ouketsu* (metaphoric blood stagnation). Women with a *qi* stagnation pattern, for example, would be more likely to respond to another commonly used formula, *kamishoyosan*. The substantially more dropouts in the treated rather than the placebo group suggests that a problem existed with the treatment itself in American women. The prominent diarrhea noted by 20% of American women receiving TU-025 at approximately 6 weeks of treatment is consistent with a constitutional state and formula mismatch.

A third concern is the appropriate dosing of the product. TU-025, keishibukuryogan, does not have active marker ingredients for monitoring. In the absence of pharmacokinetic data and monitoring capacities, no rational guidance for determining total dose and dose frequency required for a non-Japanese population exists. Dosing for this study was based on extrapolation from Japanese tradition adopted for American women with distinct preference for twice-a-day pill dosing and a higher mean BMI. Although a higher total dose was used in one arm, the dose may not have been sufficient or sufficiently frequent to effect a change.

Future trials of traditional Asian medicines will need to consider these three concerns. Most importantly, however, for future trials, Watanabe et al[30] have recently proposed two innovative methodologies that would include the use of both Western and Kampo diagnoses with randomization and placebo controls. These new methodologies not only may meet the FDA requirements for generalizable inclusion criteria but would also match traditional clinical assessments and treatments. Future studies on one of these templates should be developed. In addition, because pharmacokinetic data cannot be developed on formulas without a known, single active ingredient, smaller preliminary dose-escalation trials may be necessary to develop rational dosing guidelines.

CONCLUSIONS

Unlike clinical experience in Japan, for American women, the use of a standardized 1,800-year-old traditional Japanese multiherb formula, termed kesihibukuryogan, or TU-025, did not significantly reduce the frequency and severity of hot flash symptoms, improve climacteric symptoms, or benefit sleep quality. Also, unlike clinical experience in Japan, significant diarrhea developed in 20% of participants receiving the active agent. Despite the use of a 1-week placebo lead-in to minimize placebo response, the placebo agent significantly reduced hot flash severity and frequency. This study identified several potentially significant methodological factors unique to the scientific study of a traditional herbal formula to be considered in future assessments of traditional Asian medicines.

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Correspondence

Whaling: quota trading won't work

Anti-whaling organizations are often presented as conservationists (*Nature* **481,** 114; 2012). But for conservation efforts to advance, we need to resolve the differences between animal welfare, which is concerned with individuals, and environmental conservation, which focuses on maintaining populations, species and ecosystems.

Anti-whaling organizations spend millions of dollars every year trying to stop the Japanese whaling fleet from hunting the common minke whale (*Balaenoptera acutorostrata*), which is not endangered (*Nature* **481,** 139–140; 2012). Their use of financial resources is justifiable only from an animal-welfare perspective.

If the anti-whaling lobby were interested in whale conservation, it would use its financial power to help to assess the population ecology and dynamics of the many whale species listed as 'data deficient' by the International Union for Conservation of Nature. This would enable evidence-based quotas to be set for countries that choose to exploit this resource.

The quota-trading scheme proposed by Christopher Costello and his colleagues is a promising market-based solution for whale conservation, but is unlikely to succeed. For some countries, such as Japan, whaling is a symbol of national and cultural identity, so the economic returns may not provide sufficient incentive. Also, this is strictly a moral issue for the anti-whaling lobby, driven not by environmental conservation but by the suffering imposed on individual whales.

Over the past decade, the two sides have grown further apart. If a compromise is to be reached, environmental conservationists must inform decision-makers and public opinion in the same way that the anti-whaling lobby has used its financial muscle to push its agenda over the years.

Diogo Veríssimo, Kristian Metcalfe *Durrell Institute of Conservation and Ecology, University of Kent, Canterbury, UK. dv38@kent.ac.uk*

Scientists cannot compete as lobbyists

Suggestions that scientists should run for political office or campaign to promote their work are counterproductive and ultimately self-defeating (*Nature* **480,** 153; 2011). Science needs a permanent pipeline into policy, not temporary windows cracked open by individual researchers.

Lobbying takes time and money: more than US$3.5 billion was spent in 2010 on lobbying US Congress members. Academic scientists simply cannot compete on that scale.

Scientists must be impartial arbiters of data, not political agents. They need to be able to negotiate with governments, irrespective of their political hue, and to advise politicians in a useful and timely way.

Scientific-liaison offices would give scientists an apolitical route to policy formation. These would have a cross-ministerial mandate to make research results accessible and enable politicians and policy-makers to reach informed decisions.

When politicians ignore science, it is a failure of our system of governance rather than of individual scientists to act as lobbyists for their research.

Brett Favaro *Simon Fraser University, Burnaby, British Columbia, Canada. bfavaro@sfu.ca*

Expand Australia's sustainable fisheries

We do not believe that marine protected areas (MPAs) currently offer effective conservation in Australia. They do not address pollution or climate change (*Nature* **480,** 151–152; 2011), and overfishing there has largely been rectified. MPAs are also inadequate for managing the major threat of introduced organisms, of which more than 400 have already been identified in Australian waters.

Terry Hughes' call to protect coral reefs from catch-and-release fishing (*Nature* **480,** 14–15; 2011), by closing a further 480,000 square kilometres of ocean in Australia's Coral Sea in addition to the adjacent 507,000 km^2 already proposed, is an example of exaggerated restriction of fishing. We contend that sustainable fisheries need to be expanded, not restricted.

Australia has well-managed fisheries but imports more than 70% of its seafood. By continuing to import while closing more of its exclusive economic zones to fishing, Australia is diverting pressure on seafood resources and the responsibility for their sustainable exploitation to other countries, most of which do not have Australia's effective governance of fishing.

Robert Kearney *University of Canberra, Australia. bob.kearney@canberra.edu.au*
Graham Farebrother *Institute for Marine and Antarctic Studies, University of Tasmania, Australia.*

Use snail ecology to assess dam impact

It is not yet clear whether dam construction in the Mekong Basin will increase the impact of schistosomiasis in the region (A. R. Blaazer *Nature* **479,** 478; 2011). We need a better understanding of the parasite's transmission ecology to improve disease prediction and to determine the best dam locations.

Comparisons with dams in other countries can be misleading. In Africa, schistosome parasites are transmitted by snails with different habitat requirements from *Neotricula aperta*, a snail that is found only in calcium-rich waters in the Mekong Basin and the sole intermediate host of *Schistosoma mekongi*.

In fact, densities of *N. aperta* have declined to undetectable levels downstream of the Nam Theun 2 dam in Laos (S. W. Attwood *et al. Ann. Trop. Med. Parasitol.* **98,** 221–230; 2004) — possibly as a result of flooding, decreased calcium levels and silting. Densities are also falling farther downstream in Thailand, even though habitats there are apparently unaffected (my unpublished observations).

Stephen W. Attwood *Sichuan University, Chengdu, China. swahuaxi@yahoo.com*

Asian medicine: a way to compare data

To help to integrate traditional Asian medicine with Western medicine (S. Cameron *et al. Nature* **482,** 35; 2012), the World Health Organization (WHO) is developing common systems for collecting statistics from both. This information — known as the International Classification of Traditional Medicine (see go.nature.com/mv3iux) — is being incorporated into a revision of the WHO International Classification of Diseases, to be released in 2015.

Clean, standardized data from several countries will allow proper comparison of the effectiveness, cost and safety of the different approaches.

Kenji Watanabe, Xiorui Zhang, Seung-Hoon Choi *WHO ICTM Project Team, Center for Kampo Medicine, Tokyo, Japan. watanabekenji@a6.keio.jp*

CONTRIBUTIONS

Correspondence may be sent to **correspondence@nature.com** after consulting the guidelines at **http://go.nature.com/cmchno**.

Correspondence

Asian medicine: Japan's paradigm

The international medical community could benefit from the wide range of therapeutic options that traditional Japanese Kampo medicine can offer. Its integration into modern medicine has already been realized in Japan (*Nature* **480,** S96; 2011), where it is available as a 5-year specialization for physicians already trained in Western medicine.

Kampo and traditional Chinese medicine have common roots, but Kampo uses additional diagnostic techniques and more rigorously controls the quality of herbal preparations.

It would be a major loss for both Western and traditional medicines if political or financial factors were to cause the "sun to set" on Kampo.

Silke Cameron *University Medicine Göttingen, Germany. silke.cameron@med.uni-goettingen.de*
Heidrun Reissenweber *Clinic for Japanese Medicine, Munich, Germany.*
Kenji Watanabe *Center for Kampo Medicine, Keio University School of Medicine, Tokyo, Japan.*

Asian medicine: a fungus in decline

Estimates of wildlife trade for traditional Asian medicine should include that of the caterpillar fungus *Ophiocordyceps sinensis* (*Nature* **480,** S101–S103; 2011).

The fungus, used to treat asthma and other diseases, is legally harvested on a huge scale in Tibet and the Himalayas, and is one of the world's most expensive natural medical resources. Some 85–185 tonnes are collected annually by the local population for a global market worth between US$5 billion and $11 billion.

Large increases in the price (up by 900% from 1997 to 2008) and trade of caterpillar fungus have encouraged more intensive harvesting. My informal survey of harvesters in the Himalayas reveals that caterpillar fungus abundance is dwindling: the average harvest per collector dropped by around half between 2006 and 2010. Harvesters are extending their range as a result, risking overexploitation of a pristine landscape and more ecosystem degradation.

Conservation efforts must be initiated to halt the decline of this species, which is causing a loss of biodiversity and threatening local livelihoods.

Uttam Babu Shrestha *University of Massachusetts, Boston, USA. ubshrestha@yahoo.com*

Asian medicine: many unique types

The different branches of traditional Asian medicine are frequently confused (*Nature* **480,** S81–S103; 2011). Now could be the time to revive the centuries-old term 'Eastern medicine' to avoid such inaccuracies and to complement descriptions of Western medicine.

'Oriental' and 'Asian' medicine collectively describe the range of traditional treatments used in many Asian countries. Traditional Chinese medicine is more specific. Although practised mainly in China, it influenced the development of traditional medicines unique to Japan, Korea and Vietnam in the past few hundred years. Lumping all of these together as 'traditional Chinese medicine' is therefore incorrect.

The term 'Eastern medicine' was first coined in 1613 by a court physician in Korea, Heo Jun, in his book *Donguibogam* ('Principles and Practice of Eastern Medicine'). The book is still used in clinics and, in 2009, was added to the United Nations Educational, Scientific and Cultural Organization's World Documentary Heritage list.

Hoyun Lee *Health Sciences North, Sudbury, Ontario, Canada. mhlee@hsnsudbury.ca*

Asian medicine: call for more safety data

Marketing of traditional Chinese medicines is developing rapidly worldwide (*Nature* **480,** S81–S103; 2011). So much so that the European Union (EU) issued a directive in 2004 that all herbal preparations should be subject to the same screening procedures as pharmaceuticals by 2011. But by April last year, no Chinese herbal medicines had met the directive's requirements. Many have therefore been withheld from sale in the EU.

If these traditional remedies are to be accepted, their quality needs to be standardized and rigorous scientific data must be supplied on their efficacy and safety. The mystique surrounding such treatments must give way to verification and a proper understanding of concepts and applications. Only then can traditional Chinese medicine be integrated into a global health-care system.

Juncai Xu, Min Liu *Shanghai Clinical Research Center, Shanghai, China.*
Zhijie Xia *Shanghai Huashan Hospital, Fudan University, China. janexia2006@126.com*

Asian medicine: protect rare plants

As the global market in traditional Chinese medicines expands, many wild plants are on the brink of extinction (see also *Nature* **481,** 265; 2012). Urgent measures must be taken to ensure that these rare plants are harvested sustainably.

Some 11,000 plant species are listed in the Chinese pharmacopoeia, medicinal botany textbooks and ancient Chinese medical texts such as the *Compendium of Materia Medica* and Shennong's *Classic of Materia Medica*.

Examples of critically depleted natural populations include *Herba epimedii*, a herb used as an aphrodisiac, tonic and antirheumatic in China, Korea and Japan; *Panax ginseng*, a tonic and sleep-inducer; *Euchresta japonica*, for anti-tumour activity; *Dysosma versipellis*, a cleanser of toxins; and *Aconitum brachypodum*, an anti-inflammatory.

Hua-Feng Zhang *Shaanxi Normal University, Xi'an, Shaanxi, China.*
Xiao-Hua Yang *Xi'an Jiaotong University, Xi'an, Shaanxi, China; and Moscow State University, Russia. yxh@bk.ru*

Safety-test initiatives for nanomaterials

Your report on the need to establish safety regulations for nanomaterials focuses largely on US initiatives (*Nature* **480,** 160–161; 2011). Other initiatives are also making important contributions.

The Organisation for Economic Co-operation and Development (OECD) provides guidance on what parameters should be used for reporting the safety testing of nanomaterials (see go.nature.com/yiaxnd). Projects set up to aid implementation of Europe's REACH (for 'registration, evaluation, authorisation and restriction of chemicals') legislation advise on how to review information on nanomaterials.

The European Food Safety Authority published guidance last year on risk assessment of nanotechnologies in the food chain (see go.nature.com/7131fo). The European Commission's Joint Research Centre has also set up a repository of representative nanomaterials samples.

Juan Riego-Sintes *European Commission Joint Research Centre, Institute for Health and Consumer Protection, Ispra, Italy. juan.riego-sintes@ec.europa.eu*

Global Views 结合医学概览

Introduction of the World Health Organization project of the International Classification of Traditional Medicine

Peng-fei Gao[1], Kenji Watanabe[2]
1. Department of Traditional Chinese Medicine, Jinshan Hospital, Fudan University, Shanghai 200540, China
2. Center for Kampo Medicine, Keio University School of Medicine, Tokyo, Japan

Abstract: The World Health Organization plans to incorporate "traditional medicine" into the next revision of its International Classification of Diseases — Version 11 (ICD-11). If traditional medicine is included in ICD-11, it is definitely an epoch-making issue. The expected result is the International Classification of Traditional Medicine, China, Japan and Korea Version (ICTM-CJK). The intention of the ICTM project is not only beneficial for traditional medical components, but also might be beneficial for Western biomedicine. For this shared purpose, China, Japan and Korea must understand the meaning of this project and collaborate to develop it.

Keywords: Western medicine; medicine, traditional; International Classification of Traditional Medicine; World Health Organization

Although traditional Chinese medicine (TCM) occurs all over the Asian world, most countries like China, Korea and Japan have its own "flavor" of traditional medicine. Korean and Japanese traditional medicines originated from ancient China (Han Dynasty)[1]. Today, however, each country's traditional medicine is unique in many aspects. For example, the Korean traditional medicine (Han medicine) values four types of body constitutions (Sasang constitution diagnosis), while in Japan, Kampo medicine developed uniquely during the Edo period (1603—1867)[2].

Traditional medicine has been used in some communities for thousands of years[3]. As traditional medicine practices are adopted by new populations, there are challenges emerging. Traditional medicine practices have been adopted in different cultures and regions without the parallel advances of international standards and methods for evaluation. This kind of diversity among traditional medicine is very common so the World Health Organization (WHO) emphasizes international diversity in regard to the challenge of policies for traditional medicine.

1 WHO and traditional medicine

In 1978, the Alma-Ata Declaration on Primary Health Care called on countries and governments to include the practice of traditional medicine within their primary health care approach. Thirty years later, traditional medicine is even more

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Correspondence: Kenji Watanabe, MD, Professor; Tel: 03-5366-3824; E-mail: toyokeio@sc.itc.keio.ac.jp

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widely available, affordable, and commonly used in large parts of Africa, Asia and Latin America. For example, in some Asian and African countries, 80% of the population depends on traditional medicine for primary health care. Recent studies conducted in North America and Europe indicated that traditional medicine health care approaches tend to be used primarily in groups with higher levels of income and education[4] and in many cases, the costs are not covered by medical insurance schemes. This is not the "poor man's alternative" to Western medical care. The use of these complementary and alternative medicine (CAM) therapies has become a multi-billion dollar industry that is expected to continue its exponential growth. For instance, 70% of the population in Canada and 80% in Germany have used CAM. The most recent WHO resolution on traditional medicine (2009) urges its member states to formulate national policies, regulations and standards, as part of their comprehensive national health systems, to promote the appropriate, safe and effective use of traditional medicine to strengthen the health systems ability to provide primary care.

2 WHO activity for traditional medicine

WHO founded the Department of Traditional Medicine in 1972. Among the seven regional offices, the West Pacific Regional Office (WPRO) and the African Regional Office have a Department of Traditional Medicine, respectively. The aim of these offices is to promote traditional medicine throughout the world. Among the traditional medicines in the world, the Chinese, Korean and Japanese traditional medicines originate from ancient China, Ayurvedic medicine has Indian origin and Unani medicine is used in Arabic countries. These are considered to be the three major traditional medicines in the world, but sometimes Tibetan medicine is included, as a fourth major traditional medicine. The process of harmonization of Chinese, Korean and Japanese traditional medicines with Western medicine started in 1989 to determine the coding system of acupuncture, which was published by WHO headquarters in 1989. After that, the activity of the WPRO (key countries include China, Japan and the Republic of Korea) mainly focuses on a classification of traditional medicine in China, Korea and Japan. The aim for this activity is to include traditional medicines as a part of the next revision of the International Classification of Diseases (ICD), namely, ICD-11.

3 WHO Family of International Classification

WHO Family of International Classification (WHO-FIC) is the society which deals with international classifications. The central core classifications are ICD and International Classification of Functioning (ICF). Derived classifications contain the core classification in ICD and detailed classification in its own. Related classifications are independent from each other and maintained independently.

WHO-FIC has an annual meeting to maintain and revise the family of classifications. The proposal for the International Classification of Traditional Medicine (ICTM) to become a derived or related member of the WHO-FIC was presented to the WHO-FIC annual meeting in Tunis in October 2006. Although at the beginning there was a negative atmosphere concerning traditional medicines, the WHO-FIC supported the proposal and recommended that a formal submission should be prepared at last.

The main issues arising from WHO-FIC 2006 were as follows: (1) name of the classification should be ICTM-China, Japan and Korea (ICTM-CJK); (2) mapping of the clinical diseases section to ICD-10; (3) based on the result of these mappings, recommendations on derived or related status of the proposed classification; (4) custodianship with WPRO; (5) preparation of a draft of the classification including clinical conditions and disease patterns for the 2007 WHO-FIC meeting.

4 Mapping between ICTM-CJK and ICD-10

A second informal consultation on development of the classification was held in Tokyo, Japan, in

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March, 2007. It was held to further explore the feasibility of the proposed ICTM as a derived or related member of the family based upon the outcome of mapping between International Standard Terminologies (IST) and ICD-10 and the results of national efforts were presented by representatives from China, Japan, Korea and Vietnam. China found that only 17 of 564 IST terms (3%) could be found in ICD-10, mainly in "Infectious", "Parasitic" and "Other" chapters. They also reviewed four glossaries of TCM and found between 5% and 10% of words occurring in ICD-10. Japan did not map IST and Western medicine names as practitioners of Kampo medicine use ICD-10 for naming diseases. Japan concluded that coding independently in ICD-10, International Classification (IC)-Kampo and Kampo "SHO" (means "pattern" or "syndrome" in English) was possible from the patient charts. Korea undertook the mapping of 565 preferred terms (disease concepts) from IST to Korean Classification of Disease in Oriental Medicine (KCDOM) and ICD-10. They found 296 matches with KCDOM and 1 806 with ICD-10 (average of 6.1 ICD-10 terms to each IST term). Of 2 439 KCDOM codes, 376 were identical to IST. From Korea there was also a report of a hospital trial of disease name mapping between KCDOM and ICD-10 in 2 040 patients. The results showed that it was difficult and invalid to map between ICD-10 and KCDOM. The conclusion from Korea was that IST and ICD-10 have multiple matchings for each other. However, some areas such as ophthalmology showed 1 : 1 matching. Vietnam focused its attention on syndrome mapping and developed a Vietnamese classification of terms. It recognized that traditional medicine practitioners have access to disease names in Western as well as traditional medicines. As the mapping between IST and ICD-10 has yielded such low correspondence, it was decided to proceed with an ICTM/WPRO that could stand alone as a classification or function as Chapter 23 of ICD-10. Based on the results during the second informal consultation of development of ICTM-CJK, core members of this project met in Brisbane, Australia on August 26-29, 2007 and made the product. This product was presented in WHO-FIC annual meeting in Trieste, Italy on October 28-November 3. The product was well accepted in principle and approved as a member of related classification of WHO-FIC with the condition of some minor revisions.

5 From WPRO to the WHO headquarter

The third and final informal consultation on development of ICTM-CJK meeting was held in Seoul on Jun 24-26, 2008. After this meeting, this project was driven by the WHO headquarter. In May 2009, WHO headquarter invited various countries dealing with traditional medicine from all over the world and explained the WHO's plan to incorporate traditional medicine into ICD-11 and asked them whether they are interested in joining the project or not. Among traditional medicines in the world, the candidate for ICD-11 should be internationally used and should have systematic diagnostic ways. Because in China, Korea and Japan, traditional medicine has an inter-country experience and experience of harmonization, it met the criteria. Also, considering that the time is limited for the revision of ICD-11, WHO decided to consider Chinese, Korean and Japanese traditional medicines at the beginning. In May 2010, the first WHO meeting on the ICTM was held in Hong Kong on May 25-29[5] followed by an informal consultation on the ICTM project plan held in Geneva on March 22-24, 2010[6]. In the Hong Kong meeting, an organization was formed and it discussed how to promote this project.

5.1 Purpose of this project WHO proposed to coordinate various streams of work to develop a standardized traditional medicine terminology and classification system which will allow for regular data collection and comparisons with conventional health information systems.

5.2 Existing resources for traditional medicine classification and terminology China used the 1995 classification and codes of diseases and Zheng (pattern/syndrome) of TCM (GB95), which has disease and pattern names. It is a national standard and is distributed electronically. Also some information of interventions was included in GB97. Korea used the KCD4 (2004) based on the ICD-10 for Western medicine. The KCDOM-2 (1994) had disease names used for traditional medicine insurance claims and pattern names, and the KCDOM 2004 focuses on disease patterns. KCDOM-3 started in January 2010, designing double coding of Western disease name (ICD) and traditional medicine patterns/diseases. Japan used the ICD for disease description for Western and Kampo medicine and government insurance claims. It has also developed disease patterns for prescribing 148 formulae within Kampo medicine.

5.3 Characteristics of ICTM This project is expected to promote traditional medicine as a main stream medicine by recording all traditional medicine terminologies in ontology software (i.e. Protégé), establishing links to the current ICD and using a common base for terms when possible, producing an ICTM and linking the traditional medicine ontology/terminology and classification with other WHO-FIC products, such as cross-links to the International Classification of Health Interventions (ICHI)[7].

5.4 Benefits of the project When this project is completed, it will link traditional medicine practices with global norms and standard development activities for health information systems through the WHO-FIC. Incorporation in WHO classifications will enhance international public health tasks on global statistics, surveillance and patient safety. It will also enhance basic and clinical research around traditional medicine, which will facilitate enhanced acceptance. These project

activities will also create an international platform and a network for sharing knowledge and securing cultural sensitivity.

5.5 Challenges of this project ICTM will be made by the effort of China, Japan and Korea. However, inclusion in ICD-11 will be a big challenge because ICTM should be understood by Western physicians. Also, content models (information platforms) should be shared. This is a big challenge because the basic concepts of medicine are different between Western medicine and traditional medicine. First, medical practice is deeply connected with culture. There are large differences between Western and oriental cultural background. Second, traditional and conventional medical systems are totally different. It is not so easy to understand Chinese, Japanese and Korean traditional medicines from the viewpoint of Western medicine. Finally, if ICTM will be included in ICD-11, many challenges will remain before true integration can occur, because most of the Western physicians are skeptically regarding traditional medicine for its clinical evidence, mechanism of action and active components.

6 Conclusion

In order to promote the integration of Western and traditional medicines and provide a better health care system to the world, a shared platform is necessary. WHO ICD-11 is a good opportunity to realize this goal. Although this project is not easy, it is worth to be promoted. For this purpose, collaboration and communication of the related countries are essential.

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8 Competing interests

The authors declare that they have no competing interests.

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WHO 传统医学国际疾病分类项目介绍

高鹏飞[1], Kenji Watanabe[2]

1. 复旦大学金山医院中医科, 上海 200540

2. Center for Kampo Medicine, Keio University School of Medicine, Tokyo, Japan

摘要: 世界卫生组织计划在“国际疾病分类第 11 版(International Classification of Diseases-11, ICD-11)”中加入“传统医学”这一部分,预期的版本是“传统医学国际分类-中日韩三国版”。传统医学加入 ICD-11,有非常重大深远的意义。传统医学的国际分类的建立,不仅有利于传统医学,也有利于西方医学。所以,中、日、韩三国必须充分理解这个项目的意义和难得的现实机遇,相互进行密切合作来实现这一目标。

关键词: 西医学; 医学, 传统; 传统医学疾病分类; 世界卫生组织

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Clustering for Visual Analogue Scale Data in Symbolic Data Analysis

Kotoe Katayama[a*], Rui Yamaguchi[a], Seiya Imoto[a], Keiko Matsuura[b], Kenji Watanabe[b], Satoru Miyano[a]

[a]*Human Genome Center, Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan*
[b]*Center for Kampo Medicine, Keio University School of Medicine, 35 Shinano-machi, Shinjuku-ku, Tokyo 160-8582, Japan*

Abstract

We propose a hierarchical clustering for the visual analogue scale (VAS) in the framework of Symbolic Data Analysis(SDA). The VAS is a method that can be readily understood by most people to measure a characteristic or attitude that cannot be directly measured. VAS is of most value when looking at change within people, and is of less value for comparing across a group of people because they have different sense. It could be argued that a VAS is trying to produce interval/ratio data out of subjective values that are at best ordinal. Thus, some caution is required in handling VAS. We describe VAS as distribution and handle it as new type data in SDA.
In this paper, we define "VAS distribution" as new type data in SDA and propose a hierarchical clustering for this new type data.

Keywords hierarchical clustering; Distribution Valued Data

1. Introduction

The visual analogue scale (VAS) has developed to allow the measurement of individual's responses to physical stimuli, such as heat. The VAS is a method that can be readily understood by most people to measure a characteristic or attitude that cannot be directly measured. It was originally used in the field of psychometrics, and nowadays widely used to assess changes in patient health status with treatment. VAS is very useful to measure the changes in sensation within a patient, but it is difficult to compare more than one patients. Some researches tried to compare VAS among groups. They based on the premise of knowing the group[3],[9]. It has not argued how we

* Corresponding Author
Email address: k-kata@ims.u-tokyo.jp

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divide the group. In this study, we define VAS as distribution and develop a new clustering method to this dataset directly using Symbolic data analysis.

2. Symbolic data analysis (SDA)

Conventional data analysis usually can handle scalars, vectors and matrices. However, lately, some datasets have grown beyond the framework of conventional data analysis. Most statistical methods do not have sufficient power to analyze these datasets.
Symbolic data analysis (SDA) proposed by Diday [2],[4] is an approach for analyzing new types of datasets. "Symbolic data" consist of a *concept* that is described by intervals, distributions, etc. as well as by numerical values. The use of SDA enriches data description, and it can handle highly complex datasets. This implies that complex data can be formally handled in the framework of SDA. However, most SDA works have dealt with only intervals as the descriptions and are very few studies based on this simple idea. The case that *concept* is described by intervals is simple, but ignores detailed information in the intervals. We propose distribution-valued data to describe the *concept*.

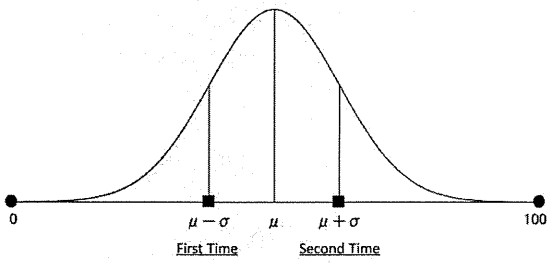

Figure 2Transform the Visual Analogue Scale to pre-PD

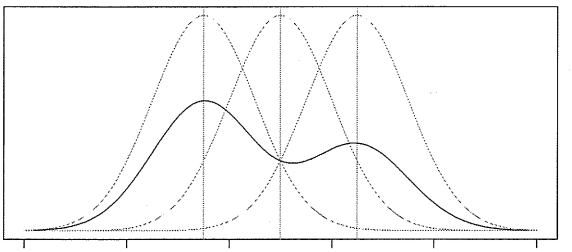

Figure 1 Transform the Visual Analogue Scale to PD: first time=35 second time=65

3. The Visual Analogue Scale (VAS)

A VAS consists of a line on a page with clearly defined end points, and normally a clearly identified scale between the two end points. For guidance, the phrase "no pain" and "worst imaginable pain" are placed at the both side of the line, respectively. Minimum value 0 of the VAS means "no pain" and maximum value 100 means "worst imaginable pain". These scales are of most value when looking at change within patients, and are of less value for comparing across a group of patients because patient have a different sense of pain. It could be argued that a VAS is trying to produce interval/ratio data out of subjective values that are at best ordinal. Thus, some caution is required in handling such data. Many researchers prefer to use a method of analysis that is based on the rank ordering of scores rather than their exact values, to avoid reading too much into the precise VAS score.

4. Transform the Visual Analogue Scale to Distribution-Valued Data

We transform the VAS to distribution-valued data. We suggest that sense of pain is described by mixture normal distribution and call it "pain distribution (PD)" Let VAS score of patient's first time be x1 and second time be x2. To define PD, we set pre-PD. We define the middle point of x_1 and x_2 as mean of each patient μ, and $(\mu - x_1)^2 = (\mu - x_2)^2$ as variance. We describe pre-PD as $N(\mu, \sigma^2)$ (Figure 1)..
Next, We set score of patient's first time x1 be mean of pre-PD as new distribution of first time (pre-PD1). New distribution of second time is defined in a similar way(pre-PD2). By combining pre-PD1 and pre-PD2, we get mixture distribution, where set mixture weight for pre-PD1 as 0.6 and for pre-PD2 as 0.4. It is, finally, PD. Figure 2 shows the case that x_1 is 35 and x_2 is 65. In case that the number of VAS score is *d,* PD is *d*-dimensional normal distribution. In this case, a diagonal matrix is used as a variance-covariance matrix of d-dimensional normal distribution.

5. Hierarchical Clustering for PD

Cluster analysis groups data objects only on the bases of information found in the data that describes the objects and their relationships. The goal is that the objects within a group should be similar (or related) to one another and different from the objects in other groups.
In this section, we propose a hierarchical clustering for distribution-valued data, especially for PD.

5.1. The Clustering Algorithm

We extend the idea of a hierarchical clustering in the framework of conventional data analysis. Let n be the number of PD and K be the number of cluster.
<Step1> Begin with K clusters, each containing only a single PD, $K = n$. Calculate distance between PD.
<Step2> Search the minimum distance in K clusters. Let the pair the selected clusters. Combine PDs into a new cluster, It is described by mixture distribution of the member, where mixture weight is equal. Let K be K-1. If $K > 1$, go to Step3, otherwise Step4.
<Step3> Calculate the distance between new cluster and other cluster, and go back to Step2.
<Step4> Draw the dendrogram.

Kullback-Leibler divergence is the natural way to define a distance measure between probability distributions [5], but not symmetry. We would like to use the symmetric Kullback-Leibler (symmetric KL) divergence as distance between *concepts*. The symmetric KL-divergence between two distributions s_1 and s_2 is

$$D(s_1(x), s_2(x)) = D(s_1(x) \parallel s_2(x)) + D(s_2(x) \parallel s_1(x))$$
$$= \int_{-\infty}^{\infty} s_1(x) \log \frac{s_1(x)}{s_2(x)} dx + \int_{-\infty}^{\infty} s_2(x) \log \frac{s_2(x)}{s_1(x)} dx \qquad (1)$$

where $D(s_1(x) \parallel s_2(x))$ is KL divergence from s_1 to s_2 and $D(s_2(x) \parallel s_1(x))$ is one from s_2 to s_1.

5.2. Distance Between PDs

In section 5.1, we use symmetric KL-divergence as distance between PDs. It is symmetric KL-divergence between Gaussian mixture distributions. However, it cannot be analytically computed. We can use, instead, Monte-Carlo simulations to approximate the symmetric KL-divergence. The drawback of the Monte-Carlo techniques is the extensive computational cost and the slow converges properties. Furthermore, due to the stochastic nature of the Monte-Carlo method, the approximations of the distance could vary in different computations.
In this paper, we use unscented transform method proposed by Goldberger, *et al*[5].

We show approximation of $D(s_1(x) \parallel s_2(x))$ in (1). Let cluster c_1 contains d-dimensional distribution $N_d\left(\boldsymbol{\mu}_m^{(1)}, \boldsymbol{\Sigma}_m^{(1)}\right) (m = 1, \cdots, M)$. Expression formula of c_1 is $s_1(\boldsymbol{x}) = \boldsymbol{\Sigma}_{m=1}^{M} \boldsymbol{\omega}_m^{(1)} \boldsymbol{p}(\boldsymbol{x}|\boldsymbol{\theta}_m^{(1)})$, where $\boldsymbol{\omega}_m^{(1)}$ is a mixture weight, $p(\boldsymbol{x}|\boldsymbol{\theta}_m^{(1)})$ is m-th probability density function of $N_d\left(\boldsymbol{\mu}_m^{(1)}, \boldsymbol{\Sigma}_m^{(1)}\right)$ and $\boldsymbol{\theta}_m^{(1)} = \left(\boldsymbol{\mu}_m^{(1)}, \boldsymbol{\Sigma}_m^{(1)}\right)$. Simmilary, cluster c_2 contains d-dimensional distribution $N_d\left(\boldsymbol{\mu}_l^{(2)}, \boldsymbol{\Sigma}_l^{(2)}\right) (l = 1, \cdots, L)$. Expression formula of c_2 is $s_2(\boldsymbol{x}) = \boldsymbol{\Sigma}_{l=1}^{L} \boldsymbol{\omega}_l^{(2)} \boldsymbol{p}(\boldsymbol{x}|\boldsymbol{\theta}_l^{(2)})$.

Approximation of KL-divergence from s1 to s2 by using unscented transform method is

$$D(s_1||s_2) \approx \frac{1}{2d} \Sigma_{m=1}^{M} \omega_m \Sigma_{k=1}^{2d} \log \frac{s_1(o_{m,k})}{s_{2(o_{m,k})}}, \qquad (2)$$

where $o_{m,t}$ are sigma points. They are chose as follows:

$$o_{m,t} = \mu_m^{(1)} + \left(\sqrt{d\Sigma_m^{(1)}}\right)_t,$$
$$o_{m,t+d} = \mu_m^{(1)} + \left(\sqrt{d\Sigma_m^{(1)}}\right)_t, \qquad (3)$$

such that $\left(\sqrt{\Sigma_m^{(1)}}\right)_t$ is t-th column of the matrix square root of $\Sigma_{\mathrm{m}}^{(1)}$. Then,

$$o_{m,t} = \mu_m^{(1)} + \sqrt{d\lambda_{m,t}^{(1)}}\,\boldsymbol{u}_{m,t}^{(1)}$$
$$o_{m,t} = \mu_m^{(1)} - \sqrt{d\lambda_{m,t}^{(1)}}\,\boldsymbol{u}_{m,t}^{(1)} \qquad (4)$$

where $t = 1, \ldots, d$, $\mu_m^{(1)}$ is mean vector of m-th normal distribution in s_1, $\lambda_{m,t}^{(1)}$ is t-th eigenvalue of $\Sigma_{\mathrm{m}}^{(1)}$ and $\boldsymbol{u}_{(m,t)}^{(1)}$ is t-th eigenvector. If $p = 1$, the sigma points are simply

$$\mu_m^{(1)} \pm \sigma_m^{(1)}$$

We can calculate approximation of $D(s_2||s_1)$. Substituting these approximations into (1), we obtain the symmetric KL-divergence. We set the divergence as distance between cluster c_1 and c_2.

5.2. Distance Between PDs

In section 5.1, we use symmetric KL-divergence as distance between PDs. It is symmetric KL-divergence between Gaussian mixture distributions. However, it cannot be analytically computed. We can use, instead, Monte-Carlo simulations to approximate the symmetric KL-divergence. The drawback of the Monte-Carlo techniques is the extensive computational cost and the slow converges properties. Furthermore, due to the stochastic nature of the Monte-Carlo method, the approximations of the distance could vary in different computations.
In this paper, we use unscented transform method proposed by Goldberger, *et al*[5].

6. An Application to the VAS Data

In this section, we apply our proposal method to real VAS data from Keio University School of Medicine. This is masked data and is not be tied to any information that would identify a patient.

6.1. Medical Questionnaire in Keio University School of Medicine

Center for Kampo Medicine, Keio University School of Medicine, have a questionnaire to patients to help medical decision. The questionnaire includes one set of questions about their subjective symptoms. There are 244 yes-no questions and 118 visual analogue scale questions,for example, "How do you feel pain with urination?". Patients answer these questions every time when they come to Keio University. Doctors can understand patients' fluctuate in severity.

6.2. Data Description and Result

For our analysis, we deal with four question: "Do you feel cold in your leg?", "Do you feel pain in your leg?", " Do you feel cold in your hand?", "Do you feel pain in your hand?". The data contain 113 patients' first and second VAS value. We transform this data set to PD. And we got some result as figures of dendrogram. The result of our simulation show in figure3. Vertical axis of this dendrogram means distance between PDs.

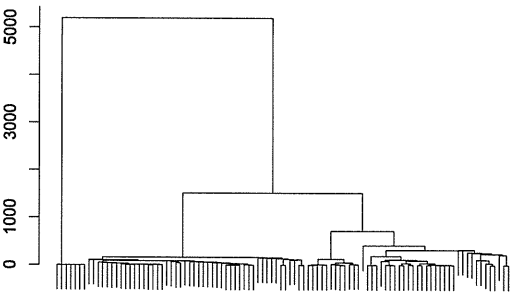

Figure 3 Dendrogram for PDs

7. Concluding Remarks

In this paper, we defined PD that is from transformation of the VAS to Distribution-Valued data. We also proposed hierarchical clustering method for it. Comparing across a group of patients by using the VAS is difficult, but our

method can do it. Through the simulation, we verified our model.
In the future, we will define multidimensional PD and apply our clustering method.

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Transform of visual analogue scale data and their clustering

Kotoe Katayama*, Rui Yamaguchi and Seiya Imoto

Human Genome Centre,
Institute of Medical Science,
The University of Tokyo,
4-6-1 Shirokanedai, Minato-ku,
Tokyo 108-8639, Japan
E-mail: k-kata@ims.u-tokyo.ac.jp
E-mail: ruiy@ims.u-tokyo.ac.jp
E-mail: imoto@ims.u-tokyo.ac.jp
*Corresponding author

Keiko Matsuura and Kenji Watanabe

Centre for Kampo Medicine,
Keio University School of Medicine,
35 Shinano-machi, Shinjuku-ku,
Tokyo 160-8582, Japan
E-mail: cherry@hop.ocn.ne.jp
E-mail: toyokeio@sc.itc.keio.ac.jp

Satoru Miyano

Human Genome Centre,
Institute of Medical Science,
The University of Tokyo,
4-6-1 Shirokanedai, Minato-ku,
Tokyo 108-8639, Japan
E-mail: miyano@ims.u-tokyo.ac.jp

Abstract: We propose a hierarchical clustering for the visual analogue scale (VAS) in the framework of symbolic data analysis (SDA). The VAS is a method that can be readily understood by most people to measure a characteristic or attitude that cannot be directly measured. VAS is of most value when looking at change within the same people, and is of less value for comparing across a group of people because they have different sense. It could be argued that a VAS is trying to produce interval/ratio data out of subjective values that are at best ordinal. Thus, some caution is required in handling VAS. We describe VAS as distribution and handle it as new type data in SDA. SDA was proposed by Diday at the end of the 1980s and is a new approach for analysing huge and complex data. In SDA, an observation is described by not only numerical values but also 'higher-level units'; sets, intervals, distributions, etc. In this paper, we define 'VAS distribution' and 'VAS changes distribution' as new type data in SDA and propose a hierarchical clustering for these new type data.

Keywords: visual analogue scale; VAS.

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Biographical notes: Kotoe Katayama received her PhD in Information Science in 2010 from the Graduate School of Information Science and Technology, Hokkaido University. She is a Project Researcher in Human Genome Centre, Institute of Medical Science, The University of Tokyo. Her research interests include multivariate statistics, symbolic data analysis, statistical inference on genomescience and bioinformatics.

Rui Yamaguchi received his PhD in 2003 from the Graduate School of Science, Kyushu University. He is a Lecturer at Laboratory of Sequence Analysis, Human Genome Center, Institute of Medical Science, University of Tokyo.

Seiya Imoto received his PhD in 2001 from the Graduate School of Mathematics, Kyushu University. He is an Associate Professor at Laboratory of DNA Information Analysis, Human Genome Center, Institute of Medical Science, The University of Tokyo. Keiko Matsuura has MD and PhD. She is a Project Assistant Professor in Center for Kampo Medicien, Keio University School of Medicine.

Kenji Watanabe is a Kampo Medicine Specialist with an MD and PhD in Internal Medicine from Keio University School of Medicine. He is a Fellow of the Japanese Society of Internal Medicine, as well as a Fellow of American College of Phisicians.

Satoru Miyano is a Professor at Human Genome Center, Institute of Medical Science, The University of Tokyo. He received his BS, MS and PhD all in Mathematics from Kyushu University, Japan, in 1977, 1979 and 1984, respectively. He joined Human Genome Center in 1996.

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1 Introduction

The visual analogue scale (VAS) has been developed to allow physical stimuli, such as heat to the measurement of individual's responses to. The VAS is a method that can be readily understood by most people to measure a characteristic or attitude that cannot be directly measured. It was originally used in the field of psychometrics, and nowadays widely used to assess changes in patient health status with treatment. VAS is very useful to measure the changes in sensation within a patient, but it is difficult to compare more than one patients. Some researches tried to compare VAS among groups. They are based

on the premise of knowing the group (Dexter and Chestnut, 1995; Price et al., 1994). However it has not argued how we divide the groups.

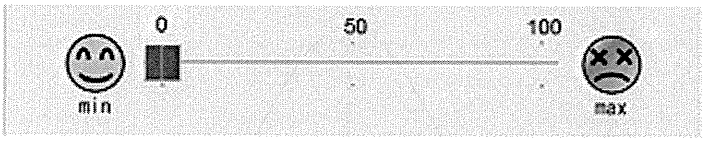
To compare VAS among groups, we transform VAS to 'symbolic data'. Symbolic data analysis (SDA) was proposed by Diday (Billard and Diday, 2006) is an approach for analysing new types of datasets. 'Symbolic data' consist of a *concept* that is described by intervals, distributions, etc., as well as by numerical values. The use of SDA enriches data description, and it can handle highly complex datasets. We propose distribution-valued data to describe the *concept.*

In this study, we define two new type of *concepts* and develop a new clustering method to them.

2 The VAS

A VAS consists of a line on a page with clearly defined end points, and normally a clearly identified scale between the two end points. For guidance, the phrase 'no pain' and 'worst imaginable pain' are placed at the both side of the line, respectively. Minimum value 0 of the VAS means 'no pain' and maximum value 100 means 'worst imaginable pain' (Figure 1).

Figure 1 Vas scale: minimum value 0 means 'no pain', maximum value 100 mean 'worst imaginable pain' (see online version for colours)



These scales are of most value when looking at change within patients, and are of less value for comparing across a group of patients because patient have a different sense of pain. It could be argued that a VAS is trying to produce interval/ratio data out of subjective values that are at best ordinal. Thus, some caution is required in handling such data. Many researchers prefer to use a method is based on the rank ordering of scores rather than their exact values, to avoid reading too much into the precise VAS score.

3 New types of *concepts*; 'PD' and 'PCD'

We define two types of *concepts*. First, we focus on sense of pain which patient naturally has. We describe the sense which patient oneself has as distribution. We name it *patient distribution* (PD). We also focus on the changes of pain within a patient and name it *patient changes distribution* (PCD).

3.1 Transform the VAS into 'PD'

We transform the VAS to 'PD'. VAS varies according to patients, because sense of pain varies a great deal depending on people. A change of VAS score within patients means their sense of pain. If they have big change of VAS score, their expression of

sense of pain is rough. On the contrary, if they have small change, their expression is sensitive. We suggest that these sense of pain is described by normal distribution and call it 'patient distribution (PD)'.

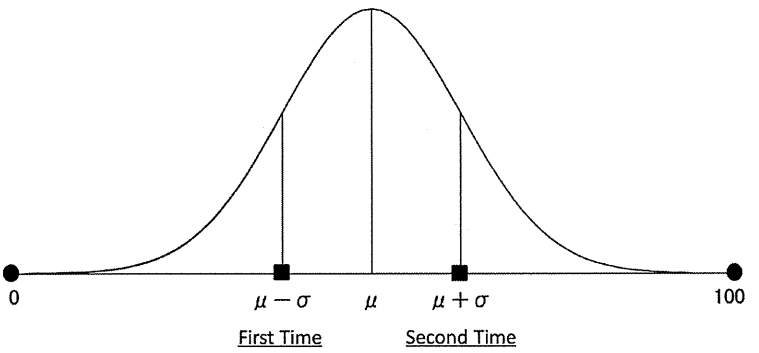
Let VAS score of patient's first time be x_1 and second time be x_2. We define the middle point of x_1 and x_2 as mean of PD μ, and $(\mu - x_1)^2 = (\mu - x_2)^2$ as variance. We describe PD as $N(\mu, \sigma^2)$. In case that the number of VAS score is d, PD is d-dimensional normal distribution. In this case, a diagonal matrix is used as a variance-covariance matrix of d-dimensional normal distribution.

3.2 Transform the VAS into 'PCD'

We transform the VAS to 'PCD' by using PD. We suggest that PCD is described by mixture normal distribution.

We set score of patient's first time x_1 be mean of PD as new distribution of first time (PD_1). New distribution of second time is defined in a similar way(PD_2). By combining PD_1 and PD_2, we get mixture distribution, where set mixture weight for PD_1 as 0.6 and for PD_2 as 0.4. This weight is based on doctors' opinions that first time VAS is more important than others. It is, finally, PCD. Figure 2 shows the case that x_1 is 35 and x_2 is 65.

Figure 2 Transform the VAS to distribution-valued data



4 Hierarchical clustering for PD and PCD

Cluster analysis groups data objects only on the bases of information found in the data that describes the objects and their relationships. The goal is that the objects within a group should be similar (or related) to one another and different from the objects in other groups.

In this section, we propose a hierarchical clustering for distribution-valued data (PD and PCD).