<table>
<thead>
<tr>
<th>Title</th>
<th>Author</th>
<th>Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validity of Time Trade-Off and Standard Gamble Assessments in Health Valuation Studies: A Study in a Multiethnic Asian Population in Singapore</td>
<td>Dr Wee Hwee Lin</td>
<td>Department of Pharmacy</td>
</tr>
<tr>
<td>Bayesian Projections of the Total Fertility Rate for All Countries in the World</td>
<td>Dr Leontine Alkema</td>
<td>Department of Statistics &amp; Applied Probability</td>
</tr>
<tr>
<td>METAL in PharMacEuTicAL: Metallodrugs for Cancer Therapy</td>
<td>Dr Ang Wee Han</td>
<td>Department of Chemistry</td>
</tr>
<tr>
<td>Electromagnetic Properties of Periodic Sub-Wavelength Metallic Structures</td>
<td>Dr Andrew Anthony Bettiol</td>
<td>Department of Physics</td>
</tr>
<tr>
<td>Organocatalytic Enantioselective Cascade Michael–Aldol Condensation Reactions: Efficient Assembly of Densely Functionalized Chiral Cyclopentenes</td>
<td>Dr Wang Jian</td>
<td>Department of Chemistry</td>
</tr>
<tr>
<td>Stem Cell Behavior and Root System Diversity in Plants</td>
<td>Dr Xu Jian</td>
<td>Department of Biological Sciences</td>
</tr>
</tbody>
</table>

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Validity of Time Trade-Off and Standard Gamble Assessments in Health Valuation Studies: A Study in a Multiethnic Asian Population in Singapore

Dr Wee Hwee Lin, Department of Pharmacy

INTRODUCTION

A variety of valuation methods have been employed in eliciting health state (HS) preferences, with choice-based valuation methods clearly preferred. Standard gamble (SG) and time trade-off (TTO) are two choice-based methods with demonstrated acceptability, reliability, and validity in Western sociocultural contexts. Both SG and TTO have established theoretical underpinnings with the former being frequently referred to as the “gold standard” because it is directly based on the axioms of expected utility theory although the latter requires the additional assumption that utility in additional healthy time is linear with respect to time. Nevertheless, TTO is preferred by some for its ease of implementation. Importantly, studies have shown that health utilities elicited by both methods are usually different, with SG typically generating higher scores. Hence, in planning studies to use choice-based preference measures such as SG and TTO in settings in which there has been relatively little experience with these measures, it is important to obtain empiric evidence with regard to validity, feasibility, and acceptability of each of these methods.

In this study, which is likely to be the first head-to-head comparison of SG and TTO methods in an Asian population, we aimed to assess the validity, feasibility, and acceptability of SG and TTO and to evaluate if systematic differences in SG and TTO scores observed in other studies were also observed in this Asian population. However, only data on validity will be reported in this newsletter due to space constrain.

METHODS

Subjects and Study Design

In this Institutional Review Board approved study, in-depth interviews were conducted among consenting Chinese, Malay, and Indian Singaporeans with at least 6 years of education in either English or their mother tongue (i.e., Chinese, Malay or Tamil) by interviewers of the same ethnic group. The various mother-tongue versions of the questionnaire were translated from the source English version using a standardized method of forward and back translations by independent native speakers of the target languages. To achieve adequate representation, two male subjects (one speaking English, the other his respective mother tongue) and two female subjects (one speaking English, the other her respective mother tongue) from each age band (20–29, 30–39, 40–49, 50–59, >60) were recruited from the Singaporean general population, giving a minimum of 20 subjects per ethnic group.

Subjects were required to perform several tasks. First, subjects expressed their preferences for three HS using SG and TTO (see sample questions in Figure 1). The HS were selected to represent varying degrees of impaired health as defined in the EQ-5D MVH protocol: mildly impaired (11122), moderately impaired (23321) and severely impaired (32313), and were administered in randomized order (sequence generated using STATA (Stata Statistical Software: Release 8. College Station, TX: StataCorp LP, 2003)). Additionally, the selected HS needed to be plausible. For example, we considered it difficult for subjects to conceive HS 31111, where apart from being confined to bed, there was no impairment on the other dimensions of health. Furthermore, each selected HS needed to have at least a level two impairment for each health dimension to increase data variability. Each HS in the EQ-5D is described by a five-digit code where each digit represents a single-item health dimension (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with value ranging from 1 (no problem) to 3 (severe problem). To ensure comparability of SG and TTO scores, we chose to rate each state on a dead-to-perfect health scale (score range 0–1) in both SG and TTO methods. On such a scale, HS regarded as worse than dead would be assigned negative scores.

Statistical Analyses

To assess the validity of SG and TTO, we hypothesized that 1) SG and TTO scores would conform to a ranked order, with lower median scores for worse HS; and 2) more subjects would rate the most severe HS as worse than dead than would rate the least severe HS as worse than dead.

To evaluate whether there were systematic differences between SG and TTO scores, we used Bland-Altman plots of the differences in utility scores (given by (TTO - SG)) against the mean utility scores (given by (TTO + SG)/2). Systematic differences would be present if the mean differences in utility scores lay outside the equivalence margins defined by the clinically important difference of 0.05 points in both directions away from zero.

RESULTS

Subjects

Of 69 subjects approached, two declined participation because they were busy and four declined after hearing that the survey involved a discussion on death. Of 63 subjects who participated (91% response rate), one 81-year-old female subject (who was a resident of a nursing home) declined to complete the section on evaluation of SG and TTO because she felt tired and was therefore excluded from the analysis.
Characteristics of subjects are summarized in Table 1.

Validity of SG and TTO

Standard gamble and TTO scores conformed to the hypothesized ranked order (Table 1), with SG scores being highest for the least impaired HS and lowest for the most impaired HS. This pattern was consistent across all ethnic groups. Interestingly, for the moderately impaired HS, ethnic differences in both SG and TTO scores were statistically significant, with Chinese assigning higher SG and TTO scores compared with Malays or Indians. In addition, as hypothesized, more subjects rated the most severe HS as worse than dead whereas the least severe HS was rated as worse than dead. This was observed for both SG (increasing severity: 8% vs. 39% vs. 59%) and TTO (8% vs. 43% vs. 62%).

Systematic Differences between SG and TTO Scores

Using Bland-Altman plots, we found systematic differences between TTO and SG scores, with differences between TTO and SG scores, with observed for both SG (increasing severity: 8% vs. 39% vs. 59%) and TTO (8% vs. 43% vs. 62%).

Using Bland-Altman plots, we found systematic differences between SG and TTO scores. We observed for both SG (increasing severity: 8% vs. 39% vs. 59%) and TTO (8% vs. 43% vs. 62%).

To the best of our knowledge, this is the first study among Chinese, Malay, and Indian Singaporeans of various ages and educational levels, both SG and TTO were valid for eliciting health preferences in this population. Nevertheless, there were systematic differences in utility scores elicited by both methods.

DISCUSSION

Hence, in this study among Chinese, Malay, and Indian Singaporeans of various ages and educational levels, both SG and TTO were valid for eliciting health preferences in this population. Nevertheless, there were systematic differences in utility scores elicited by both methods.

To the best of our knowledge, this is the first study among Asians, and provides a useful framework for comparison with future studies in other Asian sociocultural contexts. Consistent with other published studies, we found that agreement between SG and TTO utility scores was generally poor, with SG scores being generally higher than TTO scores. It was interesting that the lack of agreement was consistently evident in the three HS studied (a mild, moderate, and severe state of health).

To date, this is the only published study in Asia that concurrently evaluated both SG and TTO methods for eliciting health preferences. Our results suggest that both methods are valid and may be used in future clinical trials for direct measurement of health utility scores in this population. We recognize several limitations of this study. First, the sample study was not drawn at random from the Singapore population, which was not feasible because of cost and logistic issues. We therefore attempted to improve representativeness by specifying criteria to ensure equal gender and ethnic representation with a wide age range. Second, to reduce respondent burden, we asked subjects to evaluate only three HS each for SG and TTO, although the number of HS to be valued in existing valuation protocols typically exceeds three. Hence, generalizability of our findings to HS valuation studies involving more than three HS needs confirmation.

In conclusion, this study found both SG and TTO methods to be valid among Chinese, Malays, and Indians of various sociodemographic backgrounds. The findings are therefore likely to be applicable for population-based HS valuation studies in this multiethnic Asian population. Nevertheless, generalizability of our study findings needs to be confirmed in larger studies surveying subjects who are representative of the population being studied.

Table 1. Characteristics of Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>All (n=62)</th>
<th>Chinese (n=21)</th>
<th>Malays (n=20)</th>
<th>Indians (n=21)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Median Age (IQR)</td>
<td>43 (32, 55)</td>
<td>45 (31, 56)</td>
<td>45 (30, 51)</td>
<td>41 (35, 57)</td>
<td>0.86</td>
</tr>
<tr>
<td>Female Gender (%)</td>
<td>32 (52)</td>
<td>31 (52)</td>
<td>10 (50)</td>
<td>11 (52)</td>
<td>0.99</td>
</tr>
<tr>
<td>Median Years of Education (IQR)</td>
<td>10.0 (8.0, 13.0)</td>
<td>13.0 (10.0, 15.0)</td>
<td>10.0 (8.0, 12.0)</td>
<td>10.0 (8.0, 12.0)</td>
<td>0.019</td>
</tr>
<tr>
<td>Presence of Chronic Medical Conditions (%)</td>
<td>31 (50)</td>
<td>9 (43)</td>
<td>9 (45)</td>
<td>13 (62)</td>
<td>0.40</td>
</tr>
<tr>
<td>Working, N (%)</td>
<td>38 (61)</td>
<td>10 (48)</td>
<td>13 (65)</td>
<td>15 (71)</td>
<td>0.26</td>
</tr>
<tr>
<td>Healthcare Background (%)</td>
<td>9 (15)</td>
<td>6 (29)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0.077</td>
</tr>
<tr>
<td>Median Religiosity (IQR)</td>
<td>5.5 (5.0, 8.0)</td>
<td>5.0 (1.5, 7.0)</td>
<td>6.5 (5.0, 8.8)</td>
<td>7.0 (5.0, 10)</td>
<td>0.023</td>
</tr>
<tr>
<td>Median Standard Gamble Score (IQR)</td>
<td>0.05 (0.03, 0.05)</td>
<td>0.05 (0.04, 0.05)</td>
<td>0.05 (0.01, 0.05)</td>
<td>0.04 (0.02, 0.05)</td>
<td>0.33</td>
</tr>
<tr>
<td>Moderately Impaired</td>
<td>0.004 (-1.016)</td>
<td>0.01 (0.003, 0.03)</td>
<td>-0.50 (-1.03)</td>
<td>0.00 (-1, 0.005)</td>
<td>0.02</td>
</tr>
<tr>
<td>Severe Impaired</td>
<td>-1 (-1, 0.005)</td>
<td>0.00 (-1, 0.009)</td>
<td>-1 (-1, 0.003)</td>
<td>-1 (-1, 0.005)</td>
<td>0.31</td>
</tr>
<tr>
<td>Mildly Impaired</td>
<td>0.85 (0.45, 0.95)</td>
<td>0.90 (0.68, 0.95)</td>
<td>0.90 (0.46, 1)</td>
<td>0.80 (0.20, 0.95)</td>
<td>0.63</td>
</tr>
<tr>
<td>Severe Impaired</td>
<td>-0.18 (-0.71, 0.05)</td>
<td>0.00 (-0.61, 0.43)</td>
<td>-0.25 (-4.00, 0.06)</td>
<td>-0.33 (-0.75, 0.00)</td>
<td>0.17</td>
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† Self-reported chronic medical conditions included diabetes mellitus, hypertension, heart disease, asthma or lung diseases, bone or muscle illnesses and mental illnesses.
‡ Details of subjects with healthcare background - Chinese: 5 Pharmacy students, 1 teaching assistant in the Pharmacy department of a university; Malays: 1 office assistant in the Pharmacy department of a university, 1 cleaner in a healthcare institution; Indian: 1 hospital inpatient care assistant.
§ Standard gamble scores are rescaled on a -1 to 0 scale (see appendix).
|| Systematic Differences between SG and TTO

† Self-reported chronic medical conditions included diabetes mellitus, hypertension, heart disease, asthma or lung diseases, bone or muscle illnesses and mental illnesses.
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§ Standard gamble scores are rescaled on a -1 to 0 scale (see appendix).
||

REFERENCES

Bayesian Projections of the Total Fertility Rate for All Countries in the World

Dr Leontine Alkema,
Department of Statistics & Applied Probability

Population projections and the total fertility rate

Population projections are crucially important for many reasons. These include predicting the demand for education and medical services, pension systems, and future human impacts on the environment. The total fertility rate (TFR) is one of the key components in population projections. It is roughly the average number of children for each woman. More specifically, the TFR is a summary of age-specific birth rates within a certain period; it is the average number of children a woman would bear if she survived through the end of the reproductive age span, and experienced at each age the age-specific fertility rates of that period.

The United Nations Population Division produces estimates and projections of the total fertility rate for each country in the world. These estimates and projections are revised biannually, and published in the World Population Prospects [5]; the UN estimates of the TFR in 2005-2010 are shown in Figure 1. The estimates show that many countries in Europe and Asia have very low fertility rates, while many developing nations, especially in Africa, have much higher fertility. For example, the TFR in Singapore is currently at 1.3 children, compared to 6 children in Burkina Faso in western Africa.

Combining projections of mortality and international migration with TFR projections, the UN projects that the world population will increase to 9.1 billion people by 2050 [4]. The UN illustrates the effect of lower future fertility on future population size by subtracting half a child from the TFR projections, and similarly the effect of higher future fertility by adding half a child, which give population projections of 8 and 10.5 billion people for 2050. Though these scenarios are useful to highlight the sensitivity that a one-child difference makes on demographic outcomes, the drawback is that they do not give an assessment of the uncertainty in future fertility and therefore population levels, nor of the extent to which the low or high fertility variants are more likely. It is crucially important for policy makers to not only have a point forecast which states the most likely scenario of a future population, but also to know the range of possible future values of an outcome in order to "hope for the best while preparing for the worst".
We developed a Bayesian projection model to construct probabilistic projections of the total fertility rate for all countries in the world, as the first step to construct probabilistic population projections.

**Projecting the total fertility rate in high fertility countries**

For high fertility countries, the UN projects that fertility will decline towards replacement fertility, based on a demographic transition model [3]. In this model birth rates are expected to decrease, because of decreasing mortality and several other potential factors, including increasing access to contraception and decreasing subsistence agriculture. The fertility transition from high fertility towards replacement fertility has been observed and is currently underway in many countries around the globe. The UN models the pace of this decline in the total fertility rate as a function of its level. In the projection model, three different sets of parameter values describe three different trajectories for the pace of future declines, from which a UN analyst chooses the one which seems most appropriate for the country of interest. The UN projections for Burkina Faso are shown in Figure 2a in blue; the UN projects the TFR to decrease to 2.7 children by 2050.

The new Bayesian projection model builds onto the current UN projection model. Instead of choosing a set of decline parameters for each country, in our model these parameters are estimated for each country to obtain country-specific decline curves that represent the uncertainty in future declines. In all countries the parameter estimates are based on what has been observed historically in the country of interest, as well as observed declines in other countries that have gone through (part of) their fertility transition. This estimation approach is implemented with a Bayesian hierarchical model [2]. “Bayesian” refers to Bayesian inference; updating prior beliefs about unknown quantities based on new information. For example, in the projections for Burkina Faso, one of the unknown quantities is the maximum decrease in a 5-year period during its fertility transition. Current beliefs about this quantity can be represented with a probability distribution (its prior distribution), and new information is given by data on observed declines so far (the likelihood of each outcome being the truth). The “hierarchical” component comes in to exchange information between countries; instead of estimating the maximum decrease in each country separately, we assume that maximum decreases are comparable between countries. In the hierarchical model, the maximum decrease in each country is distributed around a world average decrease. A prior distribution is determined for the world average of the maximum decrease, and data on observed declines in all countries are used to update the world average, as well as the country-specific outcome for Burkina Faso and all other countries. A similar hierarchical approach is used for all other parameters of the decline function.

The result of this Bayesian hierarchical model is a set of estimates of the model parameters, which are used to construct a set of trajectories of future TFR outcomes. The “best” projection for the TFR is given by the median outcome of the TFR trajectories in each period, and prediction intervals are based on percentiles in that period.

Results of this approach are shown for Burkina Faso in Figure 2a. The TFR is projected to decline to 3.3 in 2050. The uncertainty of the TFR in that period is substantial; the 80% prediction interval ranges from 2.4 to 4.1 children for each woman.

**Projecting the total fertility rate in low fertility countries**

The model as discussed above is used for modelling and projecting the TFR during the fertility transition, which has been observed in many countries. Less is known about what occurs after the fertility transition has ended in low-fertility countries like Singapore. The UN projections for these countries are constructed based on the assumption that the total fertility rate will follow recent trends for the next 5 to 10 years, after which it will increase linearly (at a rate of 0.05 children per 5-year period) until it reaches 1.85 children. The UN projection for Singapore is shown in Figure 2, projecting the TFR to be 1.6 in 2050.

According to the most recent estimates, the TFR has indeed started to increase again in 50 post-transition countries. In the Bayesian projection model a time series model is used to project the future TFR after the fertility transition, based on the assumption that TFR will converge towards and fluctuate around replacement level fertility in the far future. The time series model parameters are estimated based on what has been observed so far in the 50 post-transit on countries.

Preliminary results for the projections for Singapore are shown in Figure 2b. The lower bound of the prediction interval shows that a fertility decline might still be underway, but the median TFR is projected to increase to 1.6 in 2050, with its 80% prediction interval given by [1.2, 2.1].

**Conclusions and future work**

The Bayesian projection model gives projections for the total fertility rate for each country in the world. The prediction intervals are country-specific and illustrate that uncertainty in future fertility levels differs greatly between countries; the prediction intervals are wider in most high-fertility countries because of the uncertainty in the future pace of fertility declines. The UN Population Division is now exploring the possibility of including probabilistic fertility projections in their next revision of demographic estimates and projections.

**Acknowledgements**

This is joint research with Adrian Raftery and Sam Clark (University of Washington, Seattle, USA) and Patrick Gerland, François Pelletier and Thomas Buettner (United Nations Population Division, New York, USA). For more details on the Bayesian projection model, see [1].

![Figure 2: Estimates and projections of the total fertility rate for (a) Burkina Faso, and (b) Singapore. The UN estimates and projections are shown in blue, the median projections and 80% and 95% prediction intervals as given by the Bayesian projection model are shown in red and purple.](image)

**References**

Introduction

The serendipitous discovery by Barnett Rosenberg that cis-diamminedichloroplatinum(II), more commonly known as cisplatin, can inhibit tumour growth heralded a new era of cancer research based on metallopharmaceuticals. [1] To date, cisplatin and its analogues are some of the most effective chemotherapeutic agents in clinical use and are used against a variety of malignancies including, colorectal, lung, testicular and ovarian cancers (Figure 1). The anticancer properties of this simple inorganic compound are remarkable, particularly against testicular cancer. Prior to the introduction of cisplatin, testicular cancer was a deadly disease for men with high mortality rates of approximately 70%. Platinum-based chemotherapy has dramatically reversed this trend, with curative rates exceeding 90% in early stage cases. [2] Carboplatin is a second-generation platinum drug against a similar spectrum of cancers but with lower toxicities. Oxaliplatin was approved for clinical use as recently as 2003 and used in combination with 5-fluorouracil against advanced metastatic colorectal cancers.

The cytotoxic action of these compounds requires a combination of processes including cell entry, drug activation, DNA binding and cellular responses. [3] Upon cell entry, the platinum drugs are activated by aquation and bind nuclear DNA. Formation of platinated DNA adducts lead to arrest of key cellular functions, such as transcription, and trigger a variety of cellular responses, such as repair. However, several challenges in the clinical application of these platinum-based chemotherapies remain, including their high toxicity, severe side-effects and incidence of drug resistance. These serious limitations are the driving forces behind the search for alternative chemotherapeutic strategies.

Platinum(IV) Carboxylates for Targeted Chemotherapy

One strategy to reduce toxicities and side-effects is to improve drug delivery by using targeting methods to enhance the selectivity. At the molecular level, platinum (IV) carboxylate complexes represent suitable scaffolds, since they can be readily derived from classical platinum(II) drugs without altering the pharmacophore. Upon cell entry, they are reduced by intracellular biomolecules such as glutathione, to yield cytotoxic platinum(II) moieties while releasing the axial ligands. [4] The general strategy to prepare these complexes is shown in Figure 2. The nature of the ligand sphere affects the reduction potential of the complexes and can be tuned to achieve optimal release of the platinum(II) moiety. An orally-active platinum(IV) prodrug, satraplatin, is currently undergoing phase III clinical trials for hormone refractory prostate cancer (Figure 1). Other platinum(IV) compounds with functionalised ligands have also been harnessed to defeat glutathione-transferase mediated drug resistance, target estrogen receptor-positive breast cancer and for photochemotherapy. [5]

Functionalized Organometallic Ruthenium Scaffolds

The development of ruthenium-based anticancer drugs represents one of the most prominent areas in metallopharmaceuticals for chemotherapy. [6] The main motivation for using ruthenium is its lower toxicity, in comparison to platinum, and the ease of accessing ruthenium compounds given its rich coordination and redox chemistry. Recently, two ruthenium(III)-based compounds, namely KP1019 and...
NAMI-A has successfully completed Phase 1 clinical trials and are scheduled to enter Phase 2 trials in the near future. In particular, KP1019 is transported by serum protein transferrin into cells, where it is reduced to Ru(II) species and induces oxidative DNA damage resulting in apoptosis. Another class of ruthenium complexes that have been actively pursued as anticancer agents contains the organometallic [(η6-arene)Ru] fragment (Figure 3). From a structural perspective, the organometallic ruthenium scaffold is particularly intriguing because it resembles a “piano-stool”. By altering either “stool-top” or the “stool-legs”, a range of structurally-diverse complexes can be easily prepared as targeted chemotherapeutic agents. [7] Using this strategy, a wide variety of organometallic ruthenium complexes have investigated as anticancer drug candidates and some were found to exhibit favourable pharmacological and cytotoxic profiles for further development. [8]

Conclusion and Outlook

Despite the vast amount of resources invested into the uncovering new platinum drugs for chemotherapy, there have been only few successes.

Figure 3: Synthesis of “piano-stool” organometallic ruthenium scaffold

References


This is partly due to the incomplete understanding of the mechanism of action of platinum(II)-based drugs and the reliance on conventional drug screening approaches for drug discovery. In the past two decades, tremendous strides have been made towards understanding platinum(II)-based drugs including the development of new delivery strategies based on polymers, liposomes and dendrimers. There is also increased interest in new chemotherapeutic agents based on other metal centres with the ongoing clinical evaluation of the two ruthenium complexes leading the way. While classical platinum(II)-based anticancer drugs remain the mainstays in metallopharmaceutical development, new metal-based drugs designed for selective and targeted delivery will likely dominate the scene in the near future.
Electromagnetic Properties of Periodic Sub-Wavelength Metallic Structures

Dr Andrew Anthony Bettoli, Department of Physics

Introduction

Metamaterials are artificial materials which owe their electromagnetic properties to their physical structure rather than their chemical composition. They have attracted tremendous research attention in recent years, due to their unique properties and the possibility of applications such as electromagnetic cloaking [1] and sub-wavelength imaging [2]. Metamaterials are usually composed of arrays of intricate sub-wavelength metallic structures with strong electromagnetic resonances at specific frequencies. These resonances can result in metamaterials having novel electromagnetic properties such as negative refraction (ε and μ less than zero), which was first demonstrated experimentally by Shelby et al. at radio frequencies. [3]. The metamaterial wedge used in this landmark experiment was based on the Split Ring Resonator (SRR) unit cell combined with a periodic array of metallic wires. SRRs consist of two concentric conductoring rings, each split by a gap situated oppositely (See Figure 1(a)). Although the SRRs are themselves made of a non-magnetic material such as copper or gold, they can demonstrate a band of negative magnetic permeability (μ) in a band close to their resonance frequency – a property not found in naturally occurring materials [4]. When excited by an external oscillating magnetic field, a circulating current is induced in the rings of the SRR. Due to capacitive charge accumulation at the gaps, these currents can circulate out of phase with the external driving field and result in a negative magnetic response. Negative permeability (μ) at radio frequencies can be achieved by using a periodic array of metallic strips [5]. Materials with simultaneous negative permeability (μ) and negative permittivity (ε) are sometimes referred to as left handed materials and will have a negative refractive index. Typically the unit cell dimensions of a metamaterial needs to be on the order of λ/10 where λ is the wavelength of the incident electromagnetic radiation. This makes it technically challenging to fabricate such materials as wavelengths move towards the near infra red and visible part of the spectrum. For this reason, many of the early experiments were performed at microwave frequencies.

The vast majority of metamaterials fabricated to date consist of thin, two-dimensional metallic structures that are made using planar (2D fabrication) technologies such as electron beam lithography or photolithography. Very recently however, research attention has focused on fabricating metamaterials with multiple functional layers. For example, Liu et al. reported stacking four or more SSRs using a layering technique based on electron beam writing [6]. By utilizing the novel three dimensional fabrication technologies that are available at the Centre for Ion Beam Applications (CIBA) in the Physics Department, we are investigating various types of metamaterials for applications ranging from sensing to fabricating structures that mimic quantum systems. The two key fabrication technologies that we are utilizing are proton beam writing and two photon lithography.

Sensing with metamaterials

One of the potential applications for metamaterials based on SRRs, especially at terahertz frequencies, is sensors. A metamaterial sensor takes advantage of the measurable shift in resonant frequency due to the presence of a biological or chemical sample [7]. For a two dimensional SRR array, the maximum observed frequency shift for a dielectric with permittivity of 2.7 is 30 GHz. By increasing the aspect ratio of this sensor we are able to increase the surface area at the SRR gap and as a consequence the sensitivity. This results in a frequency shift of 120 GHz for the same dielectric material [8]. Figure 2(a) shows how the resonant frequency at around 0.64 THz changes with an increase in the number of dielectric layers. The sample that we fabricated consisted of an array of several thousand SRRs over a 5x5 mm² area. Sample characterization was carried out by use of a photoconductive switch-based terahertz time domain spectroscopy (TDS) system at Oklahoma State University, USA. The measured results could be accurately reproduced using the commercially available software, MICROWAVE STUDIO™ from Computer Simulation Technologies (Shown in figure 2(b)).

Mimicking Electromagnetically Induced Transparency (EIT)

EIT refers to the phenomenon where an otherwise opaque atomic medium is rendered transparent to a probe laser beam by a second, coupling beam [9,10]. The presence of the coupling beam results in a transparency window of narrow spectral width in the absorption band. EIT occurs in three-level atomic systems and can be explained by destructive quantum interference between the pump and the probe beams, which are tuned to different transitions. In the context of metamaterials, EIT is an appealing phenomenon to study because it allows us to draw specific analogies between quantum-mechanical and classical optical systems.

We were able to achieve EIT-like behavior in a metamaterial comprised of a metallic split ring closed ring (Shown in figure 3). Individually the outer closed ring and the inner split ring show dips in the transmission spectrum corresponding to a dipole resonance and an LC resonance respectively. When combined into a single structure the material becomes transparent for a small range of frequencies within the absorption band due to the coupling between the two resonances. Simulations showing the EIT-like behavior are shown in figure 4. We fabricated the
structure using proton beam writing and measured its optical properties for THz frequencies using THz-TDS. Our results reveal that a group index as high as 75 could be obtained within the transparency band [11]. The mimicking of EIT in metamaterials is thus an attractive means to develop the building blocks of systems for slow light applications.

Figure 1: SEM image of an array of high aspect ratio gold SRRs fabricated using proton beam writing. Also shown is a simulation of the circulating currents at resonance.

Figure 2: Measured (a) and simulated (b) transmission amplitude as layers of photoresist with $\varepsilon = 2.7$ are added to a high aspect ratio SRR array [8].

Figure 3: An SRR array fabricated in gold using proton beam writing. This structure is designed to mimic the quantum phenomenon of electromagnetically induced transparency (EIT) [11].

Figure 4: Simulated transmission spectra of the double ring structure and its isolated constituents; inner split ring (a), closed outer ring (b), and double ring (c) (blue solid curve, left axis). The red dashed curve (right axis) in (c) shows additionally the phase advance [11].

References

Organocatalytic Enantioselective Cascade Michael–Aldol Condensation Reactions: Efficient Assembly of Densely Functionalized Chiral Cyclopentenes

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The development of asymmetric methods for the preparation of functionalized cyclopentenes has been of long-standing interest to organic chemists. As a result of their broad applications in organic synthesis they are widely distributed in a vast array of bioactive molecules.[1, 2] In the past, significant advances have been made in this area by using transition-metal-mediated [3+2] and [4+1] cycloaddition reactions.[3] Furthermore, stereosepecific ring opening of chiral cyclopropanes,[4] ring-closing metathesis of chiral dienes,[5] and organometallic-catalyzed Nazarov cyclizations[6] have also been described. Herein, we report a novel strategy for the preparation of chiral cyclopentenes through an organocatalytic, highly enantioselective cascade Michael–aldol condensation reaction. Significantly, the cascade sequence enables quick construction of heavily functionalized cyclopentenes with the generation of two new C-C bonds with high enantioselectivity (91–97% ee) from readily available starting materials under mild reaction conditions.

C-C bond-forming reactions are considered the most important processes in organic synthesis. Developing novel cascade reactions that achieve the formation of multiple C-C bonds in one operation is a particularly attractive strategy for the efficient construction of complex molecular architectures. The formation of more than one bond adds an environmentally friendly aspect owing to the elimination of time consuming and costly purification procedures and protection/deprotection steps.[7, 8] Having established the capacity of chiral diarylprolinol silyl ethers to catalyze asymmetric cascade Michael–aldol condensation processes by using heteroatom S, O, or N as nucleophiles for the formation of new C-X and C-C bonds (Scheme 1),[9] we sought to extend the concept for the construction of multiple C-C bonds in a one-pot transformation. The development of such processes has been a challenging task, and only few examples have been recently described.

Motivation for this study was influenced by the lack of catalytic asymmetric approaches to the Michael-aldol condensation process starting by evaluating a model reaction between trans-4-nitrocinnamaldehyde (1 a) with dimethyl 2-oxoethylmalonate (2) in the presence of 10 mol % I in CHCl₃. The cascade Michael-aldol condensation process proceeded smoothly to afford desired product 3 a in 74% yield and 89% ee. No side products were detected. Encouraged by this, we surveyed pyrrolinol ethers II and III for the reaction under the same reaction conditions. While II afforded comparable results with a slightly higher ee value, no reaction occurred for the more sterically bulky catalyst III. Screening additives including acid and bases revealed that they had an effect on the process, and the use of 0.5 equiv NaOAc gave the best result. To further determine the scope of the cascade process, examination of the reaction medium led to the selection of Cl(CH₂)₂Cl. The increased reaction yield with Cl(CH₂)₂Cl is probably due to the increased solubility of the base, which thereby favorably facilitates the enolization of the malonate moiety in 2.

Validation of the proposed cascade Michael-aldol condensation process started by evaluating a model reaction between trans-4-nitrocinnamaldehyde (1 a) with dimethyl 2-oxoethylmalonate (2) in the presence of 10 mol % I in CHCl₃. The cascade Michael-aldol condensation process proceeded smoothly to afford desired product 3 a in 74% yield and 89% ee. No side products were detected. Encouraged by this, we surveyed pyrrolinol ethers II and III for the reaction under the same reaction conditions. While II afforded comparable results with a slightly higher ee value, no reaction occurred for the more sterically bulky catalyst III. Screening additives including acid and bases revealed that they had an effect on the process, and the use of 0.5 equiv NaOAc gave the best result. To further determine the scope of the cascade process, examination of the reaction medium led to the selection of Cl(CH₂)₂Cl. The increased reaction yield with Cl(CH₂)₂Cl is probably due to the increased solubility of the base, which thereby favorably facilitates the enolization of the malonate moiety in 2.

After the optimal conditions had been established, the generality of the cascade Michael-aldol condensation processes was explored. The organocatalytic enantioselective cascade reactions serve as an efficient route for the preparation of highly functionalized cyclopentenes (Scheme 4). Significantly, the new stereogenic center is created in high enantioselectivity (91-97 % ee) in the one-pot procedure. Moreover, the process affords the formation of a new quaternary carbon center,
and significant structural variation of α, β-unsaturated aldehydes can be tolerated. The electronic nature of the aromatic rings of α, β-unsaturated aldehydes has limited influence on the stereochemical outcome. It demonstrates that the electron-withdrawing, electron-donating, combined electron-withdrawing and donating, neutral, and heteroaromatic systems can participate in the reactions. Probing the steric effect on the enantioselectivity of the cascade processes indicates that such impact is also minimal. Finally, less reactive aliphatic enals were used, and almost no reaction occurs.

In conclusion, we have described a novel organocatalytic, enantioselective cascade Michael-aldol condensation reaction. The process is efficiently catalyzed by readily available (S)-diphenylprolinol triethylsilyl ether to give synthetically useful, highly functionalized chiral cyclopentenes. The significance of the methodology is highlighted by its correlation to the protocols for the preparation of cyclohexenes, developed by the Enders and Hayashi groups. In principle, the strategy described can also be extended to the preparation of six-membered ring systems. This approach constitutes our future direction aimed at expanding the scope of the powerful cascade processes.

References:
Stem Cell Behavior and Root System Diversity in Plants

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Plants contribute significantly to the beauty of our planet and are the basis for the survival of all “higher” organisms on Earth. In the next decades, it will become increasingly important for us to learn how diverse plants develop and how they evolve in response to a rapidly changing environment, to maintain and improve the sustainability of our ecosystem.

The basic plant structure includes two organ systems: The shoot system, and the root system. The development of both systems depends largely on the activity of meristems, which are specified sections of plant tissue characterized by cell division and growth. Within these meristems, the stem cell populations are reliably maintained, for hundreds of years in some species, and continuously provide new cells for plant growth. Determining how stem cells are established and maintained in meristems is fundamental both for addressing the basic biological features of stem cell behavior and understanding diverse aspects of plant development.

Like animal stem cells, plant stem cells are self-renewing and have the potential to form many different cell types. This was best demonstrated in the root meristem of the eudicot model plant Arabidopsis thaliana, which has exceptionally simple anatomy and largely invariant cell lineage (Figure 1A), and is therefore an excellent system for studying stem cell behavior in plants. Using laser ablation method, high-resolution confocal imaging of fluorescent cell identity and auxin-responsive markers, and mutants with patterning defects, we previously investigated a local regeneration response in Arabidopsis roots\(^1\). Our study revealed essential roles for the auxin-responsive AP2/EREBP (APETALA2/ethylene responsive element binding protein) family transcription factors PLETHORA\(^1\) (PLT1) and PLT\(^2\), and the GRAS family transcription factors SCARECROW\(^3\) (SCR) and SHORTROOT\(^4\) (SHR) in controlling root stem cell behavior during regeneration, and provided a mechanism in which embryonic root stem cell patterning factors respond to and stabilizes a new auxin distribution. Such feedback mechanisms between transcription factor action and auxin distribution also occur during normal development\(^4\). Thus, like in animals, stem cell behaviour in Arabidopsis is controlled through the combinatorial activity of transcription factors.

Increasing evidence suggests that changes in transcriptional regulation can give rise to new anatomical structures and phenotypic characteristics. Specific differences in anatomy and gene expression are often correlated, and comparisons of transcription profiles among distantly related taxa point to extensive evolutionary changes in gene regulatory networks. Understanding how transcriptional regulatory systems contribute to the evolution of phenotypes represents a major challenge for evolutionary developmental biology (Evo-Devo).

An example illustrating the success of this approach is the analyses of Drosophila wingless gene and its closely related counterpart, the mouse oncogene int gene, leading to the discovery of over 100 WNT (concatenation of wingless and int) family genes throughout the animal kingdom and effective therapy for some human cancers, and revealing context-dependent cell signaling roles of a particular gene family member in different organisms. Similarly, with the complete sequence of the Arabidopsis and rice genomes and mounting evidence for extensive homology between Arabidopsis and rice genes, these two model plants now allow us to analyze the evolution of developmental mechanisms in the two major seed plant clades: the eudicots and the monocots.

The rice root system consists of a seminal (primary) root and numerous crown roots and lateral roots (Figure 2). Unlike Arabidopsis, post-embryonic shoot-borne crown roots form the major rice root system. Lateral roots in rice are initiated from pericycle and endodermis, whereas Arabidopsis lateral roots arise completely from pericycle. In addition, rice roots have a different meristem anatomy compared to Arabidopsis roots (Figure 1B). First, clear differences in tissue organization exist. The ground tissue of rice roots consists of increasing layers of cortical cells (approximately up to 15) and one endodermal cell layer, whereas Arabidopsis roots have only one cortical and one endodermal cell layer. Furthermore, rice and Arabidopsis roots have different spatial organization of stem cell niches. For example, in Arabidopsis roots two sets of tissues, the epidermis/Lateral root cap (LRC) and the ground tissue (cortex/endodermis), each derive from a single stem cell, whereas in rice roots the epidermis and LRC do not share common progenitor stem cell, and cortex/endodermis stem cell activity is resumed in meristematic endodermal cells which divide again to produce additional cortex layers. This suggests that regulation of the stem cell niche can be highly flexible, allowing for evolutionary innovations.

Rice has several major advantages over other model monocot species such as maize. It has a small genome size, and the complete sequence of the rice genome is now available. Rice is the most readily transformable cereal crop and increasing number of rice T-DNA insertion lines has been generated for reverse genetic studies. Furthermore, the development of molecular and genetic tools and functional genomics resources for rice is rapidly moving forward. This provides an excellent opportunity for us to study stem cell behavior and root system diversity in plants. The knowledge and information derived from our research can lead to a rational manipulation of root architecture. The ability to manipulate root architecture and growth will allow us to design novel molecular genetic breeding approaches in major monocot crops such as orchids.

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**Academic Profile:**
Dr. Xu Jian received his PhD in Molecular Cell Biology from Utrecht University, the Netherlands in 2005. After 3 years of postdoctoral training at the same university, he joined the Department of Biological Sciences as an assistant professor in January 2009. During his PhD and postdoctoral research, Dr. Xu discovered for the first time a molecular framework for plant regeneration, and contributed significantly to our current view of the molecular and cellular mechanisms of polar transport of the important plant growth hormone auxin. He published his research extensively in top-tier journals including two SCIENCE and three NATURE papers, and his pioneering work won him several prestigious awards, including the Veni Award 2008 from the Netherlands Organization for Scientific Research (NWO) and the National University of Singapore (NUS) Young Investigator Award 2009.

**Research Interests:**
- Environmental and developmental regulation of root architecture in plants
- Molecular and cellular mechanisms of regeneration in plants
- Polar auxin transport and pattern formation in plants

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Figure 1: Schematic representation of the Arabidopsis (A) and rice (B) root meristem, median longitudinal view. Cells in green: quiescent center (QC) cells; Cells in pink: endodermal cells. Note that QC cells define the stem cell niche and cells surrounding the QC are root stem cells.

Figure 2: 7-day-old rice (left) and Arabidopsis (right) seedlings. SR: seminal (primary) root; CR: crown root; LR: lateral root; PR: primary root. Photograph from Chen Ya.