Detecting temperature fluctuations at equilibrium

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The Gibbs and the Boltzmann definition of temperature agree only in the macroscopic limit. The ambiguity in identifying the equilibrium temperature of a finite-sized ‘small’ system exchanging energy with a bath is usually understood as a limitation of conventional statistical mechanics. We interpret this ambiguity as resulting from a stochastically fluctuating temperature coupled with the phase space variables giving rise to a broad temperature distribution. With this ansatz, we develop the equilibrium statistics and dynamics of small systems. Numerical evidence using an analytically tractable model shows that the effects of temperature fluctuations can be detected in the equilibrium and dynamical properties of the phase space of the small system. Our theory generalizes statistical mechanics to small systems relevant in biophysics and nanotechnology.

Using maximum entropy arguments, we first estimate the joint equilibrium distribution $p_{eq}(\vec{r},\beta)$ by introducing two new intensive parameters in a hyperensemble. We then show how our theory reduces to traditional statistical mechanics of macroscopic systems in a suitable limit. We illustrate connections of our theory with the non-extensive statistical mechanics of Tsallis at thermodynamic equilibrium. Then, we propose Fokker–Planck and Langevin equations for the time evolution of the instantaneous distribution $p(\vec{r},\beta,t)$. Finally, using realistic all-atom molecular dynamics simulations, we present numerical evidence to support our framework and discuss its limitations.

Theory

As above, consider a small system. Due to possible non-weak coupling between the system and the bath, the equilibrium phase space distribution of the system $p_{eq}(\vec{r})$ will depend on the nature of system–bath interactions. Let us work with the ansatz that the non-canonical behavior arises because the temperature of the system fluctuates. The joint equilibrium distribution is simply

$$p_{eq}(\vec{r},\beta) = p_{eq}(\vec{r}|\beta) \times p_{eq}(\beta).$$

(1)

In eqn (1),

$$p_{eq}(\vec{r}|\beta) = e^{\beta(F(\beta) - H(\vec{r}))}$$

(2)

is the usual Boltzmann distribution and $p_{eq}(\beta)$ needs to be determined. Here, $F$ is the free energy and $H$ is the temperature independent Hamiltonian of the system. Since there are no conservation laws for temperature, the Gibbs’ ensemble picture is inapplicable. We resort to an equally valid alternative. We employ the maximum entropy (maxEnt) framework.

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We maximize the entropy of the joint distribution \( P(r, \beta) = P(r|\beta) \times p(\beta) \) subject to suitable constraints. The entropy of the joint distribution is given by

\[
S[p(r, \beta)] = - \sum_{r, \beta} p(r, \beta) \log p(r, \beta)
\]

(3)

\[
= - \sum_{\beta} p(\beta) \log p(\beta) + \sum_{\beta} s(\beta)p(\beta)
\]

(4)

where

\[
s(\beta) = - \sum_{r} p(r|\beta) \log p(r|\beta).
\]

(5)

\[
p(\beta) = \sum_{r} p(r, \beta)
\]

(6)

is the marginal of \( p(r, \beta) \), and \( p(r|\beta) \) is given by eqn (2).

When determining \( p_{eq}(\beta) \), the choice of constraints is important. Since the temperature of the system is not fixed, we choose \( \beta \) as a constraint. Also, while the entropy of the composite macroscopic system comprising the system and the surrounding bath is maximized, the entropy of the small system itself is not. Consequently, we choose the average entropy \( s(\beta) \) as an additional constraint and maximize \( S[p(r, \beta)] \) using Lagrange multipliers. The constraint of the average entropy is common in statistical physics and Bayesian statistics of hyperensembles. See ref. 18–21 for different motivations behind this choice. After maximization, we find that the equilibrium distribution \( p_{eq}(\beta) \) is estimated by

\[
p_{eq}(\beta) = \frac{e^{\lambda s(\beta) - \beta \lambda}}{Z(\lambda, \zeta)}.
\]

(7)

In eqn (7),

\[
Z(\lambda, \zeta) = \int e^{\lambda s(\beta) - \beta \lambda} d\beta
\]

(8)

is a generalized partition function and \( \lambda \) and \( \zeta \) are Lagrange multipliers that determine the shape of \( p_{eq}(\beta) \). If the entropy \( s(\beta) \) is a unitless number, then \( \lambda \) is unitless and \( \zeta \) has the units of \( 1/\beta \). The physical interpretation of these Lagrange multipliers will become clearer below.

The joint equilibrium distribution \( p_{eq}(r, \beta) = p_{eq}(r|\beta) \times p_{eq}(\beta) \) is

\[
p_{eq}(r, \beta) = \frac{e^{\beta F(r) - \beta \lambda s(\beta) + i \lambda \zeta}}{Z(\lambda, \zeta)}
\]

(9)

Thus, instead of describing a thermally equilibrated small system with one intensive parameter, its inverse temperature \( \beta \), our framework requires two intensive parameters \( \lambda \) and \( \zeta \) whose meaning will become clear below.

Connection to traditional statistical mechanics

Assume that the entropy \( s(\beta) \) is monotonically decreasing with \( \beta \), a reasonable assumption for systems with monotonically increasing density of states. A straightforward calculation shows that the maximum of \( p_{eq}(\beta) \) is situated at \( \beta = \beta_0 \), where \( \beta_0 \) is such that \( \lambda \zeta = -c(\beta_0)/\beta_0 \). Here,

\[
c(\beta_0) = \frac{ds(\beta_0)}{d\beta} \bigg|_{\beta=\beta_0}
\]

(10)

is the heat capacity of the system when interacting with an ideal gas at inverse temperature \( \beta_0 \).

In the limiting case, when \( \lambda \rightarrow \infty \) and \( \zeta \rightarrow \infty \) such that their ratio is constant, a non-negligible contribution to \( p_{eq}(\beta) \) comes only from near \( \beta = \beta_0 \) and \( p_{eq}(\beta) \approx \delta(\beta - \beta_0) \), where \( \delta(x) \) is the Dirac delta function. This is exactly the traditional canonical ensemble picture where the system is assigned the temperature of the surrounding thermal bath. It is clear that the magnitudes of \( \lambda \) and \( \zeta \) dictate the breadth of the \( p_{eq}(\beta) \) distribution and hence the deviation from the canonical ensemble. The ratio \( \lambda/\zeta \) dictates the most likely temperature of the system.

Connection to non-extensive statistical mechanics

Systems that do not obey the conventional distributions from statistical mechanics are sometimes entertained within a framework called non-extensive statistical mechanics.\textsuperscript{10} Though not commonly invoked for small systems at equilibrium, here, we will demonstrate that non-extensive statistical mechanics can be arrived at by marginalization over temperature in a hyperensemble.

Consider a system whose entropy scales as the logarithm of temperature, \( s(\beta) = s_0 \log \beta \), and the internal energy scales proportional to the temperature, \( U(\beta) = U_0 \beta \), when coupled to a bath of ideal gas particles at inverse temperature \( \beta \). These are excellent assumptions for bound systems where the density of states increases monotonically with energy. Examples include ideal gas in a container and a collection of harmonic oscillators. From eqn (7), we have

\[
p_{eq}(\beta) = \frac{e^{-\beta U_0 \zeta - i \lambda s_0 \frac{\zeta}{\beta} + 1}}{\Gamma(\lambda \zeta + 1)}.
\]

(11)

eqn (11) is a gamma distribution also known as the generalized \( \chi \)-squared distribution. Interestingly, a gamma distributed inverse temperature is very commonly used in a superstatistical interpretation of non-extensive statistics.\textsuperscript{22} Marginalizing over the gamma distributed inverse temperature in eqn (1) results in the so called “Tsallis statistics” for the phase space. We have

\[
p_{eq}(r, \beta) = \frac{e^{\beta U(\beta) - \beta \lambda s(\beta) + i \lambda \zeta}}{Z(\lambda, \zeta)}
\]

(12)

\[
= \frac{e^{\beta U_0 - \beta(\lambda s_0 + \zeta) + (i - 1) s_0 \log(\beta)}}{Z(\lambda, \zeta)}.
\]

(13)

Integrating over \( \beta \), we have

\[
p_{eq}(r) \propto (1 - \beta_0(q - 1) \lambda s_0)^{-1/\lambda s_0}
\]

(14)
eqn (14) is the \( q \)-generalized canonical ensemble distribution in Tsallis statistics where
\[
q = \frac{s_0 - \lambda}{s_0 - \lambda - 1} \quad \text{and} \quad \beta_0 = \frac{\lambda - s_0 + 1}{\beta}.
\]

In the framework of non-extensive statistical mechanics, one arrives at eqn (14) by maximizing Tsallis’ entropy with respect to \( p(r) \) by constraining an unnatural escort expectation of energy.\(^{\text{10}}\)

When deriving \( p_{\text{eq}}(r) \) by maximizing the non-extensive Tsallis entropy, one needs to constrain unnatural expectation values known as escort expectation values.\(^{\text{23}}\) In contrast, in this work, we derive it from a superstatistical distribution eqn (9) and additional assumptions about \( p_{\text{eq}}(\beta) \) and system behavior. In our derivation, the gamma distribution \( p_{\text{eq}}(\beta) \) arises in a context specific manner i.e. through the logarithmic dependence of the entropy on the inverse temperature and by constraining the average inverse temperature. Therefore, starting from the extensive Gibbs–Shannon entropy, maxEnt can act as a predictive framework for constructing non-extensive effective entropies of which the Tsallis entropy is a particular example.

Previously, non-extensive entropies have been criticized from an Occam’s razor point of view\(^{\text{16,24–26}}\) when compared to the extensive Gibbs–Shannon entropy, maxEnt can act as a predictive framework for constructing non-extensive effective entropies of which the Tsallis entropy is a particular example.

Stochastic dynamics

For simplicity of notation, let us consider a one-dimensional system. The simplest time evolution of the instantaneous distribution \( p(r; \beta; t) \) of the extended phase space that relaxes to a prescribed equilibrium distribution \( p_{\text{eq}}(r; \beta) \) can be modeled by an overdamped Smoluchowski equation. We have
\[
\frac{\partial p(r; \beta; t)}{\partial t} = -\left( \frac{1}{\gamma_r} \partial_r [f_r \cdot p] + \frac{1}{\gamma_\beta} \partial_\beta [f_\beta \cdot p] \right) + D_r \frac{\partial^2 p}{\partial r^2} + D_\beta \frac{\partial^2 p}{\partial \beta^2}
\]
(16)

where the ‘forces’ \( f_r \) and \( f_\beta \) are defined as
\[
f_r = \frac{\partial}{\partial r} \log p_{\text{eq}}(r; \beta) \quad \text{and} \quad f_\beta = \frac{\partial}{\partial \beta} \log p_{\text{eq}}(r; \beta).
\]
(17)

By construction, eqn (16) will relax to the equilibrium distribution \( p_{\text{eq}}(r; \beta) \) if \( D_r = 1/\gamma_r \) and \( D_\beta = 1/\gamma_\beta \). Note that the statistical properties of \( (r(t), \beta(t)) \) can also be estimated by an overdamped Langevin equation (Brownian dynamics) that is equivalent to eqn (16). The Langevin equation reads
\[
\dot{r} = D_r f_r + \sqrt{2D_r} \eta_r
\]
\[
\dot{\beta} = D_\beta f_\beta + \sqrt{2D_\beta} \eta_\beta
\]
(18)

Here, \( \eta_r \) and \( \eta_\beta \) are usual uncorrelated Gaussian random variables with unit variance.

Given the coupled nature of \( r(t) \) and \( \beta(t) \), we do not expect \( r(t) \) to be purely diffusive on the so-called ‘free energy landscape’ which is the negative logarithm of the \( \beta \)-marginalized equilibrium distribution of \( r(t) \). This non-diffusive behavior is automatically captured by eqn (16) in addition to predicting the equilibrium properties of \( r(t) \). In contrast, traditional statistical mechanical approaches only estimate the free energy landscape. The non-diffusive dynamics is modeled independently of the equilibrium properties, for example, by assuming inhomogeneous diffusion coefficients\(^{\text{27}}\) or dynamically fluctuating free energy landscapes.\(^{\text{28}}\)

Linear analysis

It is instructive to study a linear system before analyzing realistic molecules. Consider a one-dimensional harmonic oscillator interacting with a thermal bath. If the deviations from a canonical distribution are negligible, we can treat eqn (17) in the linear regime by expanding \( f_r \) and \( f_\beta \) to the first order in \( r \) and \( \beta \). In the linear approximation, the joint equilibrium distribution \( p_{\text{eq}}(r, \beta) \) will be described by a joint normal distribution. The simplest coupled system of the overdamped Langevin equations for \( r(t) \) and \( \beta(t) \) that relaxes to a joint normal distribution is given by
\[
\dot{r} \approx l_{11} r + l_{12} \beta + \eta_r
\]
\[
\dot{\beta} \approx l_{21} r + l_{22} \beta + \eta_\beta
\]
(19)
(20)

We have assumed that the variables \( r \) and \( \beta \) are appropriately scaled by absorbing the diffusion constants \( D_r \) and \( D_\beta \), \( l_{11} \) are the scaled linear expansion coefficients of \( f_r \) and \( f_\beta \), and \( \eta_r \) and \( \eta_\beta \) are the usual uncorrelated Gaussian noises. Integrating over \( \beta(t) \) and substituting in \( r \), we get
\[
\dot{r} = l_{11} r + l_{12} \beta + \eta_r
\]
\[
+ l_{12} e^{l_{22} t} \int_0^t ds \cdot \eta_r e^{-l_{22} s} + \eta_r
\]
\[
\Rightarrow \dot{r} = (l_{11} + l_{12} \beta + (l_{12} l_{22} - l_{11} l_{22} \dot{r}) + \eta_r
\]
(21)
(22)

The time derivative of white noise \( \eta_r \) is purple noise, which has a quadratically increasing power spectrum. The dynamics of temperature fluctuations are governed by the linear terms \( l_{12} \), \( l_{21} \), and \( l_{22} \), and white noise \( \eta_r \). These terms also appear in the effective Langevin equation for \( r(t) \). The linear analysis suggests that one can infer the dynamics of \( \beta(t) \) by observing the dynamics of \( r(t) \).

The dynamics of \( r(t) \) are governed by a much richer equation than the usual overdamped Langevin equation. A one-dimensional small linear harmonic oscillator exchanging energy with a thermal bath can be modeled by a second-order Langevin equation with a combination of white and purple noise. These predictions can be
tested by observing the dynamical properties of a small colloidal particle trapped in a harmonic well using optical traps.

**Numerical evidence**

How do we verify the effects of temperature fluctuations in the phase space of a small system? We resort to realistic molecular dynamics simulations of an analytically tractable system viz. a harmonic oscillator.

Consider a three-dimensional dumbbell-shaped Lennard-Jones harmonic oscillator interacting non-weakly with a bath. Realistic examples include colloidal beads tied to each other by a biopolymer or linear molecules such as CO₂. The canonical ensemble distribution for the Harmonic oscillator is given by

$$p_{eq}(\beta) = \frac{4\beta^{3/2}r^2}{\sqrt{\pi}} \times e^{-\beta r^2}$$  \hspace{1cm} (23)

where $r$ is the displacement of the oscillator. Without loss of generality, we have assumed that the spring constant of the oscillator is $k = 2$. If the system–bath interactions are non-negligible, we expect that the equilibrium phase space distribution for the oscillator will deviate considerably from the Boltzmann distribution.

The entropy of the oscillator scales as $s(\beta) \sim \log \beta$, and from eqn (7) we know that the equilibrium distribution $p_{eq}(\beta)$ will be governed by a gamma distribution

$$p_{eq}(\beta) = \frac{e^{-\beta r^2} \beta^{2\lambda+1}}{\Gamma(\lambda+1)}.$$  \hspace{1cm} (24)

The joint equilibrium distribution $p_{eq}(r,\beta) = p_{eq}(r|\beta) \times p_{eq}(\beta)$ on the other hand is obtained by multiplying eqn (23) and (24)

$$p_{eq}(r,\beta) = \frac{4\beta^\lambda r^2 e^{-\beta r^2}}{\sqrt{\pi} \Gamma(\lambda+1)}.$$  \hspace{1cm} (25)

Integrating over all values of $\beta$, we obtain the marginal $r$ distribution

$$p_{eq}(r) = \frac{4\beta^\lambda r^{2\lambda+1} \Gamma(\lambda+\frac{5}{2})}{\sqrt{\pi} \Gamma(\lambda+1)}.$$  \hspace{1cm} (26)

Moreover, we can also model the dynamics of the oscillator using the coupled Langevin equation of eqn (17). From eqn (22), the “forces” $f_r$ and $f_\beta$ are given by

$$f_r = \frac{2}{r} - 2r \beta$$ \hspace{1cm} and \hspace{1cm} $$f_\beta = \frac{3 - 2\beta r^2 - 2\beta r^2 + 2\lambda}{2\beta}.$$  \hspace{1cm} (27)

eqn (26) along with eqn (18) where the forces $f_r$ and $f_\beta$ are given by eqn (27) are our predictions for the harmonic oscillator regardless of the bath it is interacting with. These predictions can be tested experimentally or in a realistic numerical simulation.

With the aid of MD simulations of a dumbbell-shaped Lennard-Jones harmonic oscillator coupled with a bath of water molecules at 300 K (see Appendix I for details) using all-atom MD simulations. The numerically obtained marginal distribution $p(r)$ of the oscillator separation $r$ is better captured by eqn (26) (red line) than the usual canonical ensemble distribution of eqn (23) (blue line).

Fig. 1 We study the equilibrium properties of a 3D dumbbell-shaped harmonic oscillator comprising Lennard-Jones particles interacting with a bath of water molecules at 300 K (see Appendix I for details) using all-atom MD simulations. The numerically obtained marginal distribution $p(r)$ of the oscillator separation $r$ (black squares) is better captured by eqn (26) (red line) than the usual canonical ensemble distribution of eqn (23) (blue line).

that eqn (26) which allows for a broad temperature distribution indeed fits the numerically estimated distribution much better than the usual canonical ensemble distribution of eqn (23). It is clear that by allowing the inverse temperature to have a broad distribution, the equilibrium properties of the harmonic oscillator interacting with its thermal surroundings are captured correctly.

The dynamics of $r(t)$ can be predicted using eqn (16) by studying the equivalent Langevin equation (see Appendix II). In Fig. 2, we compare the numerically estimated autocorrelation function

$$C(\tau) = \langle r(t)r(0) \rangle_{eq} - \langle r \rangle_{eq}^2$$  \hspace{1cm} (28)

obtained from MD simulations (black squares) and the prediction from the 2D Langevin equation (red). The predictions from an

Fig. 2 We study the autocorrelation function of the harmonic oscillator interacting with a bath of water molecules. We model the dynamics of the extended phase space $(r(t),\beta(t))$ using a simple coupled Langevin equation (see Appendix II). We find that the 2-dimensional Langevin equation (red line) captures the two time scales inherent to the dynamics of $r(t)$ as observed in MD simulations (black squares). On the other hand, an analogous 1D Langevin equation can only capture one effective time scale (blue line).
analogous 1D Langevin equation that relaxes to $p_{\text{eq}}(t)$ of eqn (26) are shown in blue. While the dynamics observed in the MD simulation have two time scales resulting in a double exponential decay of the autocorrelation function, the 1D Langevin equation is able to capture only one effective time scale. On the other hand, the 2D Langevin equation has two natural time scales governed by $D_r$ and $D_\beta$, respectively. The coupled Langevin equation equivalent to eqn (16) (see Appendix II) with $dt = 5 \times 10^{-8}$ and $D_\beta \approx 50 \times D_r$ does indeed capture the autocorrelation function, while an analogous 1D equation fails to do so (see Appendix II for details of the fit).

In this work, we study a system whose canonical ensemble distribution can be analytically computed and the entropy analytically estimated. This allowed us to compute $p_{\text{eq}}(\beta)$ and $p_{\text{eq}}(r, \beta)$ analytically. For more realistic systems with multiple degrees of freedom, $p_{\text{eq}}(r, \beta)$ needs to be estimated numerically along with $p_{\text{eq}}(\beta)$.

In summary, a mesoscopic harmonic oscillator interacting with a thermal bath of water molecules shows significant deviation from the canonical ensemble description. We can correctly predict both equilibrium and dynamical properties of the oscillator by allowing its temperature to vary as a stochastic variable which is coupled with the phase space variable $\eta(t)$.

Discussion

It is known that, at equilibrium, mesoscopic systems have larger fluctuations compared to a macroscopic system. We have argued that these enhanced fluctuations can be understood as arising from a dynamically fluctuating temperature.

How do we reconcile a time-dependent temperature, a non-equilibrium phenomenon prima facie, in an equilibrium setting? Even though the temperature is changing, the extended phase space $(\vec{r}(t), \vec{p}(t))$ is still governed by a detailed, balanced Markov process. It is an easy calculation to show that the entropy production, as defined in stochastic thermodynamics, is indeed zero for the hyperensemble. Nevertheless, there are multiple questions which need resolution. For example: How do we formulate non-equilibrium phenomena in the hyperensemble setting? and How do we modify non-equilibrium fluctuation relationships for small systems? We leave this to future work. The integration time step was 0.25 femtoseconds and the trajectory was saved every 2.5 femtoseconds.

Appendix II: fitting Langevin dynamics to data

The coupled Langevin equation corresponding to eqn (16) where the equilibrium distribution $p_{\text{eq}}(r, \beta)$ is given by eqn (24) is given by

$$
\frac{d}{dt}\begin{pmatrix} r(t) \\ \beta(t) \end{pmatrix} = \begin{pmatrix} -\frac{\Gamma}{m} r(t) + \sqrt{2\Gamma/m} \eta_r & 0 \\ 0 & -\frac{\Gamma}{\kappa} \beta(t) + \sqrt{2\Gamma/\kappa} \eta_\beta \end{pmatrix} + \begin{pmatrix} D_r f_r \\ D_\beta f_\beta \end{pmatrix} = \begin{pmatrix} D_r f_r \\ D_\beta f_\beta \end{pmatrix} + \begin{pmatrix} \sqrt{2\Gamma/m} \eta_r \\ \sqrt{2\Gamma/\kappa} \eta_\beta \end{pmatrix}.
$$

Here, $\eta_r$ and $\eta_\beta$ are uncorrelated Gaussian random variables with unit variance, $dt$ is a small time step, $D_r$ and $D_\beta$ are diffusion coefficients for the phase space coordinate $r$ and the temperature $\beta$.

From the MD simulations, we first estimated the autocorrelation function $C(t)$. The Langevin equation can be scaled in time by multiplying the diffusion constants and dividing the time step $dt$ by the same number. In order to ensure smooth integration, we first set the integration time step to a very small value; $dt = 5 \times 10^{-8}$. Every pair $(D_r, D_\beta)$ of diffusion constants predicted an autocorrelation function that had two inherent time scales manifested in a double exponential decay. We manually scanned the $(D_r, D_\beta)$-space to match the MD-autocorrelation function. We found that $D_r = 1$ and $D_\beta = 50$ gave reasonable fits (red curve).

We also wrote down a 1D Langevin equation analogous to eqn (29),

$$
r(t + dt) \approx r(t) + D_r f_r dt + \sqrt{2D_r dt} \eta_r,
$$

where $f_r = \frac{d}{dr} \log p_{\text{eq}}(r)$ (see eqn (26)). This equation had only one diffusion constant $D_r$. A one-dimensional scan of $D_r$ suggested that the autocorrelation function predicted using the 1D Langevin equation always had a single exponential decay. We found the best fit to the autocorrelation function at $D_r \approx 50$ (blue curve).

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References


Appendix I: MD simulations

A harmonic dumbbell-shaped oscillator consisting of two Lennard-Jones particles was immersed in a bath of 333 TIP3P water molecules. NVT molecular dynamics simulations were run using NAMD at 300 K with a box size of 19.12 Å. The CHARMM forcefield was used to describe the interaction between the harmonic oscillator particles and surrounding water molecules. The spring constant for the dumbbell was chosen to be $k = 0.25$ kcal mol$^{-1}$ Å$^{-2}$, the $\epsilon$ parameter was set at $\epsilon = -20.0$ kcal mol$^{-1}$ and the size parameter was set at $r = 1$ Å. The systems were minimized for 2000 steps followed by an equilibration of 1 nanosecond and a production run of 2 nanoseconds.

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References


14 P. Dixit and D. Asthagiri, Role of Local Metal-Site Interactions and Bulk Protein Restraints in the Thermodynamics of Zinc Binding to a Zinc Finger Protein, *Biophys. J.*, 2012, 102, 457.


