Symmetry Breaking in X-Chromosome Inactivation

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X-Chromosome Inactivation

Female mammal cells contain the XX combination of non-autosomal chromosomes. in order to prevent the double expression of X-linked proteins and RNA one X-chromosome is inactivated randomly.

- Each X-chromosome contains a region known as the X-inactivation-centre (*Xic*).
- The *Xic* produces X-inactivation specific transcript RNA (*Xist*).
- Each cell contains just enough of some 'Blocking-factor' (BF) to coat the future active X-chromosome (*Xa*) and prevent its silencing. [1]
- Once inactivation begins the *Xist* (initially expressed at low levels in an unstable form) begins to build up and coat the future inactive X-chromosome (*Xi*)

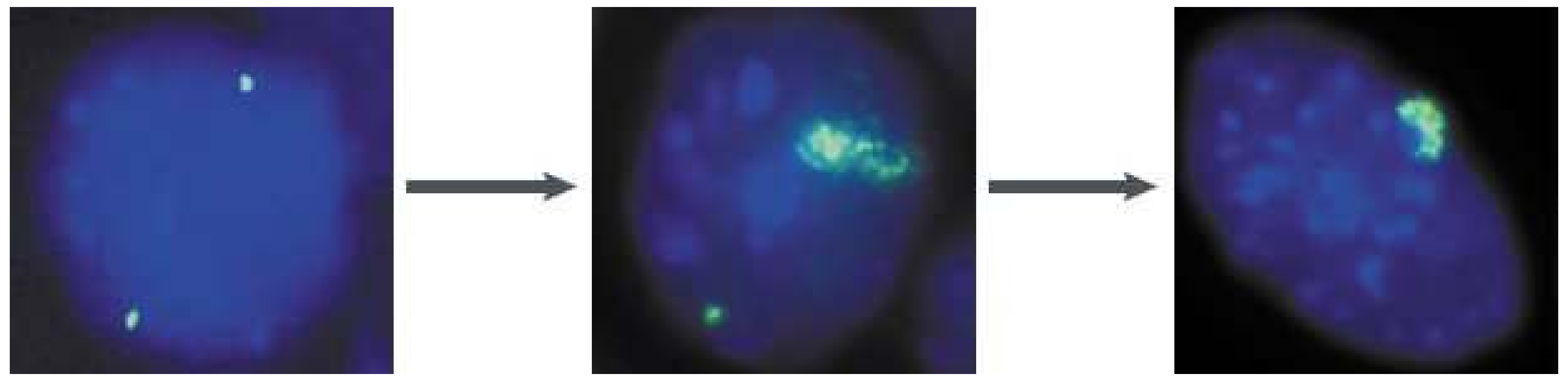

Figure 1: *The progress of XCI. The build up of stable Xist on the future inactive X-chromosome can clearly be seen. (reproduced from [2])*

Spontaneous Symmetry Breaking Model

The model studied is an on-lattice model where the BF molecules are free to diffuse around a region of space of size $2L^3$ containing the two co-localised *Xic*s. The mutual affinity between the BFs and the affinity due to the *Xic*s leads to the Hamiltonian [3]

$$\mathcal{H} = -E_0 \sum_{\langle ij \rangle} b_i b_j - E_x \sum_{\langle ij \rangle} b_i x_i$$

Where <*ij*> indicates the sum over nearest neighbour sites, b_i is 1 if the site contains a BF and 0 otherwise and x_i is defined similarly for *Xic* segments.

The order parameter, *m*, is defined as the difference between the number of BF molecules bound to the right *Xic* and the left *Xic*. A BF is "bound" if it is contained within a cylinder of radius 2.5 lattice spacings around either X-Chromosome.

$$m = \frac{|N_r - N_l|}{N_r + N_l}$$

- The model displays a thermally driven phase transition between the disordered, symmetric state (both *Xic*s uncoated) and the ordered, asymmetric state (one *Xic* coated).
- The model was investigated using **Monte-Carlo** simulation (specifically the **Metropolis algorithm**)
- The aim of this project was to investigate the nature of this phase transition, classify it as abrupt or continuous and investigate any finite size scaling effects.

[1] Sarah M. Duthie. Mechanisms of x-inactivation. Encyclopedia Of Life Sciences, 2001.
[2] Philip Avner and Edith Heard. X-chromosome inactivation: Counting, choice and initiation. Nature Reviews — Genetics, 2, 2001.
[3] Mario Nicodemi and Antonella Prisco. Symmetry breaking model for x-chromosome inactivation. Phs. Rev. Letters, 98(108104), 2007

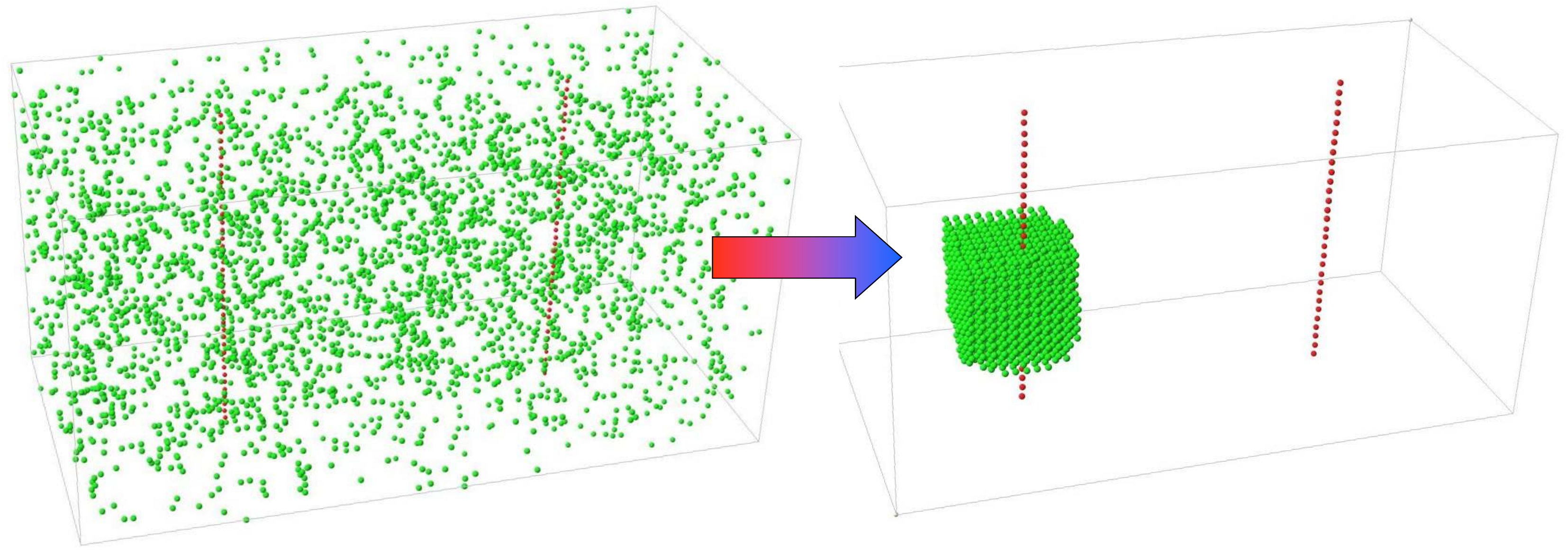

Figure 2: *Upon cooling the blocking-factors condense into a single cluster which coats a single X-chromosome.*

Results

For lattices sizes of 40 and above the phase transition can clearly be seen in the graphs of energy per BF and order-parameter vs. Temperature. It is especially clear in the order-parameter that there is a very sudden jump between the states.

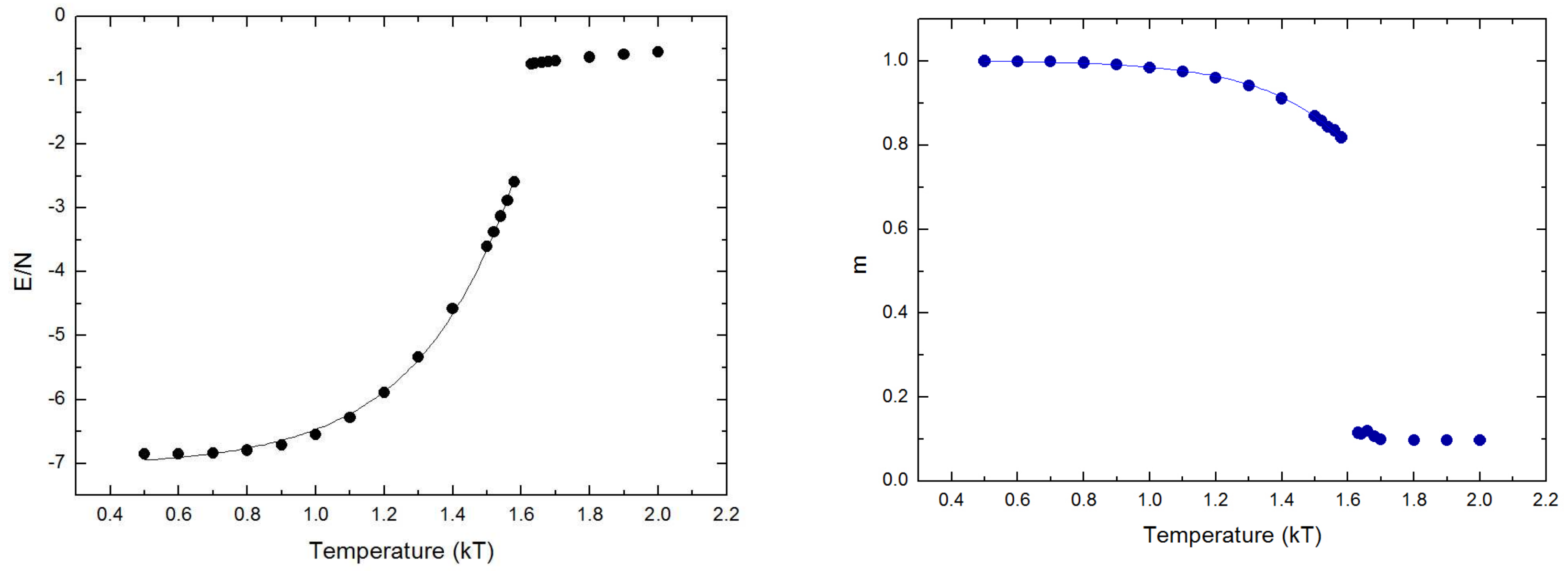

Figure 3: *Graphs of Energy per BF (left) and order-parameter (right) vs. Temperature*

The data obtained for the specific heat (C_v) and susceptibility (χ) also show the apparent abrupt nature of the phase transition. While both C_v and χ increase around T_c, crucially, they do not diverge (divergence is a signature of continuous phase transitions).

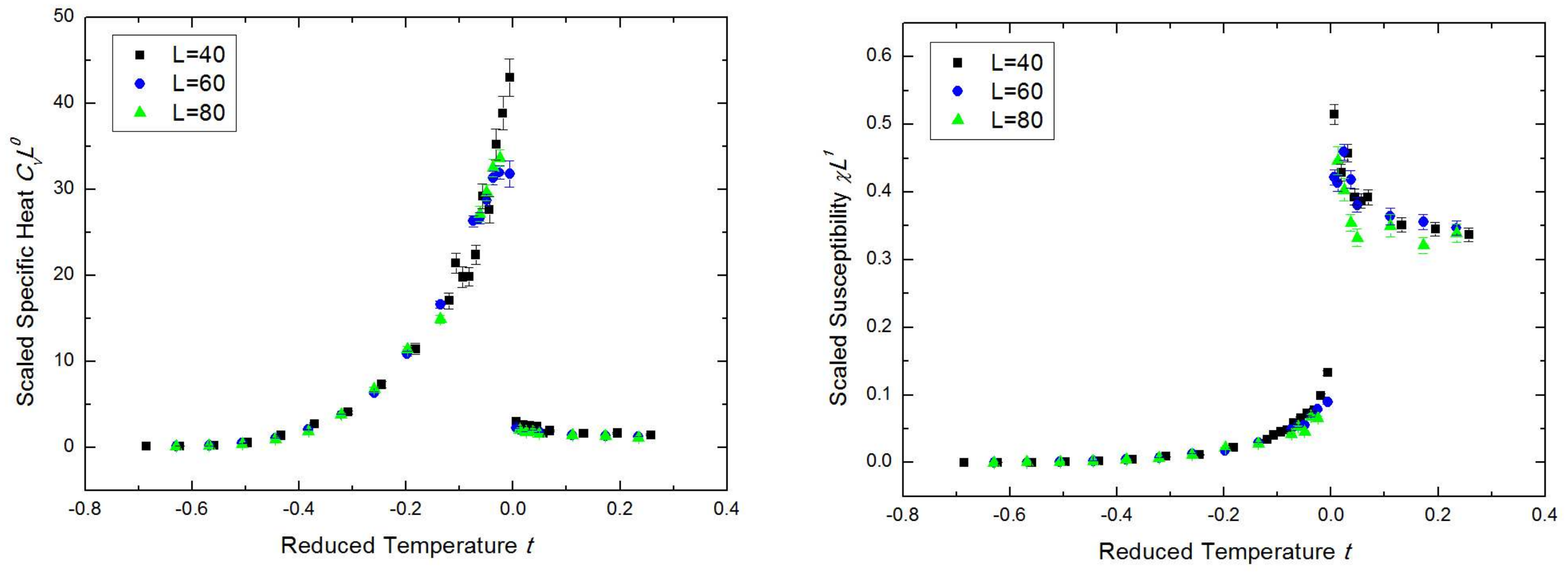

Figure 4: *Graphs of Specific heat (left) and susceptibility (right) vs. Reduced Temperature for a variety of lattice sizes.*

Finite Size Scaling

The data shown in Figure 4 comes from a variety of lattice sizes and shows how the data, when correctly scaled, collapses onto a single curve.

- Specific heat (per particle) scales as L^0 (no rescaling required)
- Susceptibility (per particle) scales as L^1
- ...a direct consequence of the number of available "binding sites" increasing linearly with *L*.
- Trivial integer exponents point to an **abrupt phase transition**.

Finite size effects also cause the critical temperature to move as lattice size is changed.

- T_c in the thermodynamic limit calculated by fitting a curve of the form $T_c(L) = T_c(\infty) - a/L$ to the measured values.
- It was found that the critical temperature at the thermodynamic limit is **1.68 (1) k_BT**.

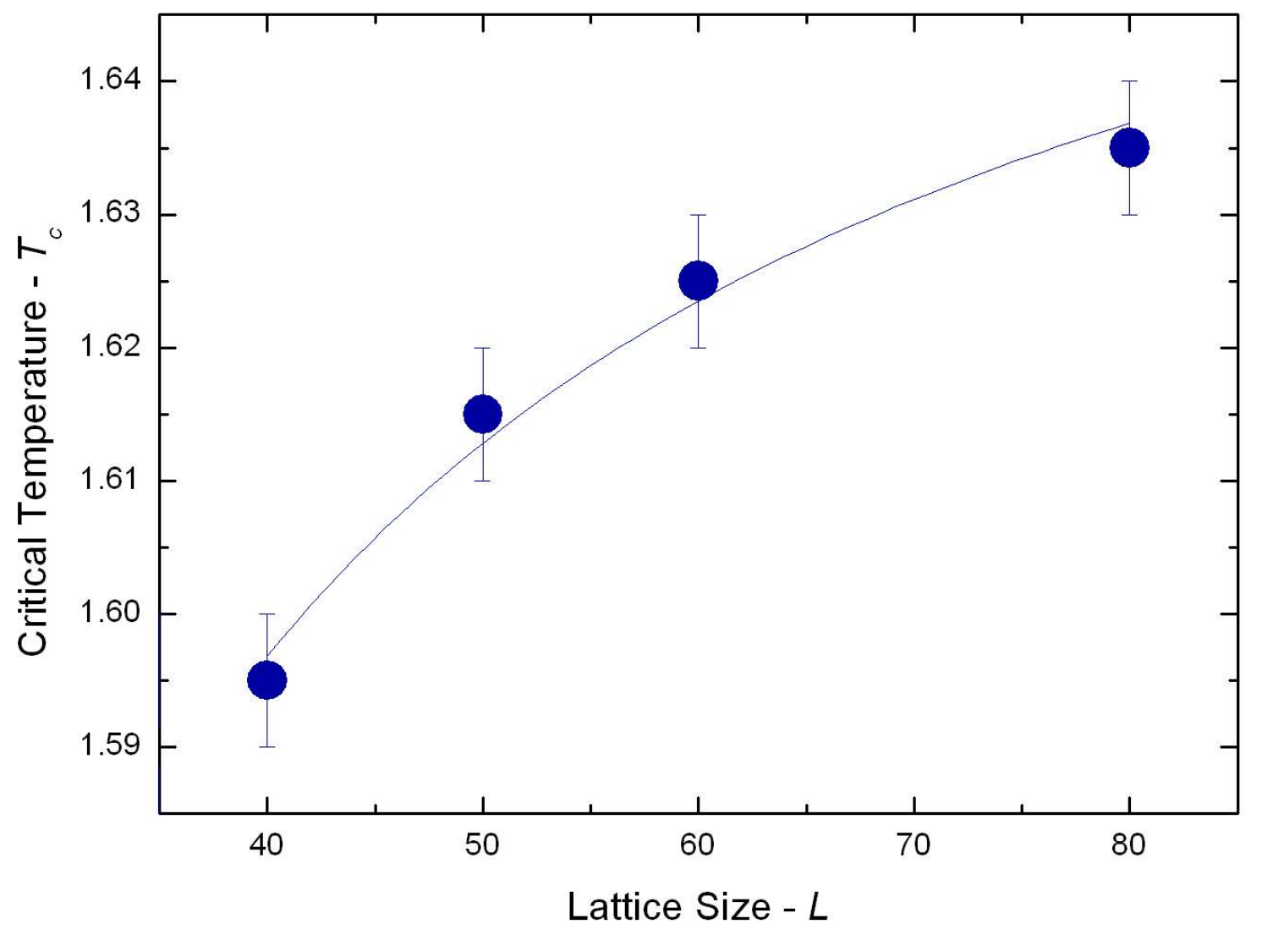

Figure 5: *Graph of critical temperature vs. lattice size*

Metastability

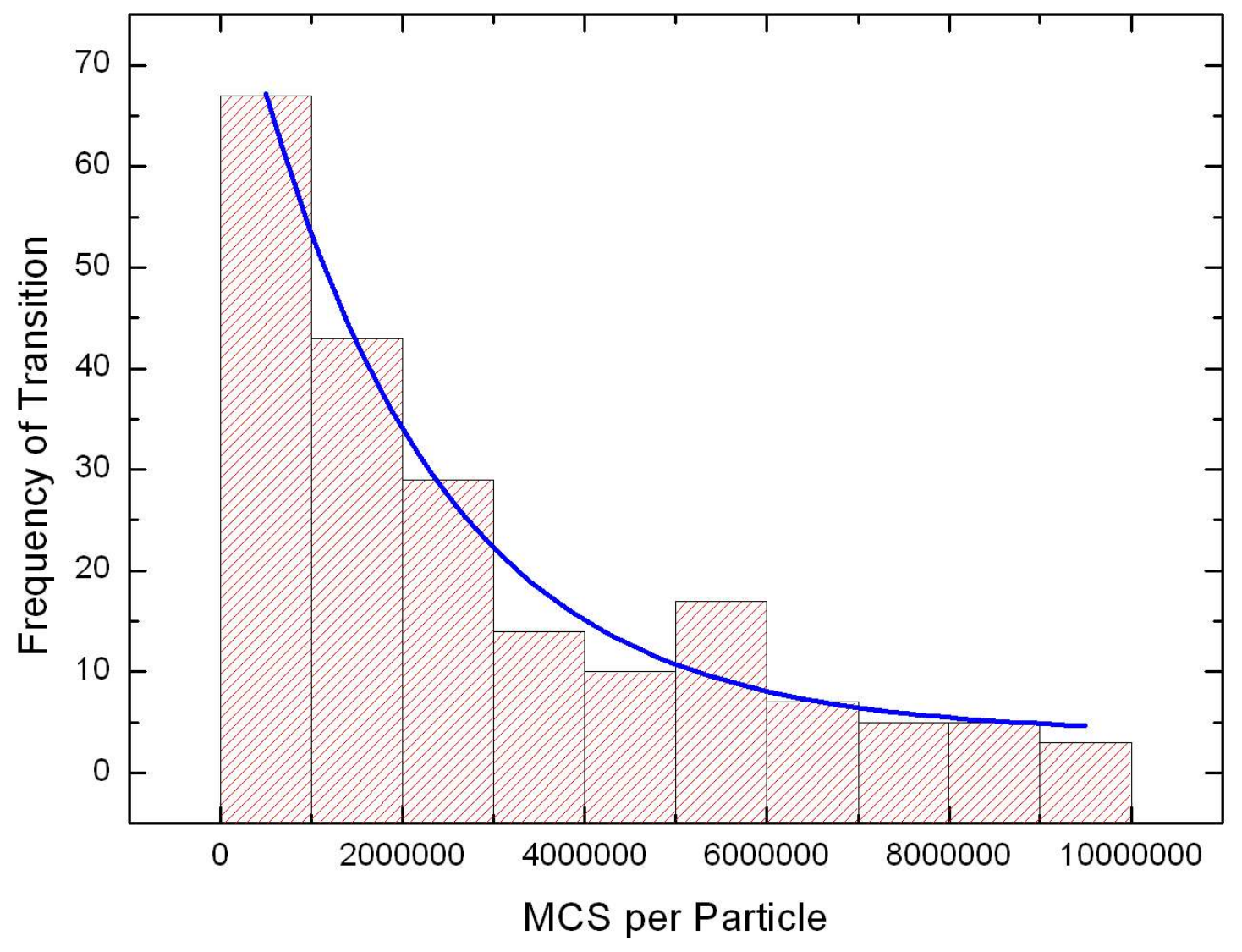

Figure 6: *Histogram showing the time at which the meta-stable state underwent the transition. ($T=1.59\ k_BT$, $L=50$)*

As with other abrupt phase transitions the energetically unfavourable states become **metastable** above (or below) T_c (c.f. Super-cooled water).

- Below T_c the system transitions to the lower symmetry state due to random fluctuations.
- The probability of staying in the metastable state decays exponentially with time (Figure 6).
- The metastability is responsible for the large value of the correlation time seen at the critical temperature.

Conclusion

The extensive computer simulations carried out through this investigation lead to the conclusion that

- The transition is an abrupt transition.
- The critical temperature is 1.68 ± 0.01 k_BT.
- The system is metastable below the critical temperature.
- The thermodynamic quantities of interest scale trivially with system size.