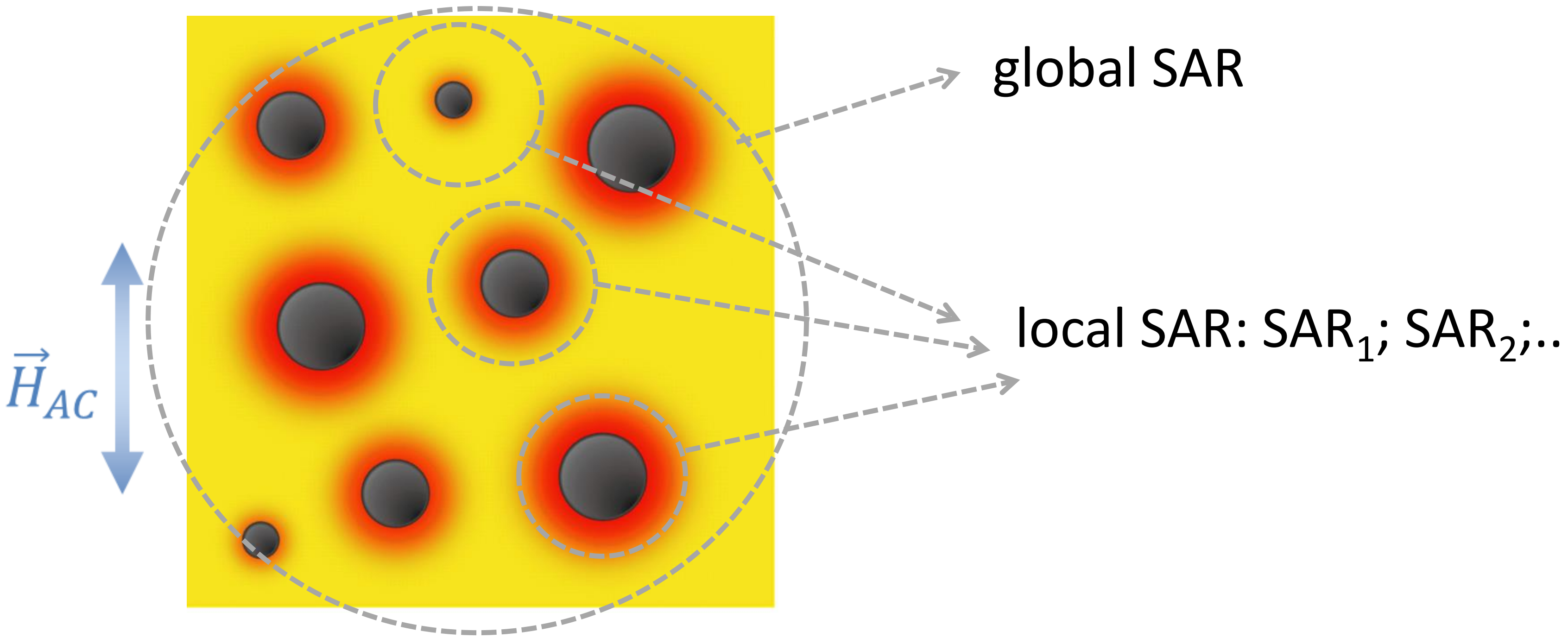
Local *vs* global heating in magnetic nanoparticle hyperthermia

C. Munoz-Menendez, D. Serantes, S. Ruta, O. Hovorka, K. Livesey, P. Nieves, O. Chubykalo-Fesenko, D. Baldomir and R. W. Chantrell

Local vs global heating

- Conventional approach assumes therapy arises from uniform heating.
- Is that the whole story?
- In the following
  - We review experimental evidence for rapid local temperature increase on the nanometre scale
  - We investigate a possible mechanism of local heating arising from individual switching events
  - Demonstrate irreversible behaviour in ‘non-switching’ particles due to interparticle interactions
  - Dynamic simulations show 3rd mechanism: heating due to precessional switching

Goal: energy dissipated by each particle - individually?



Outline

1. Motivation
2. Kinetic Monte Carlo
3. How to estimate the local heating?
4. Conclusions

Motivation

- Successful AC hyperthermia treatment with negligible SAR

EGFR-Targeted Magnetic Nanoparticle Heaters Kill Cancer Cells without a Perceptible Temperature Rise

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ARTICLE

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Hyperthermia HeLa Cell Treatment with Silica-Coated Manganese Oxide Nanoparticles

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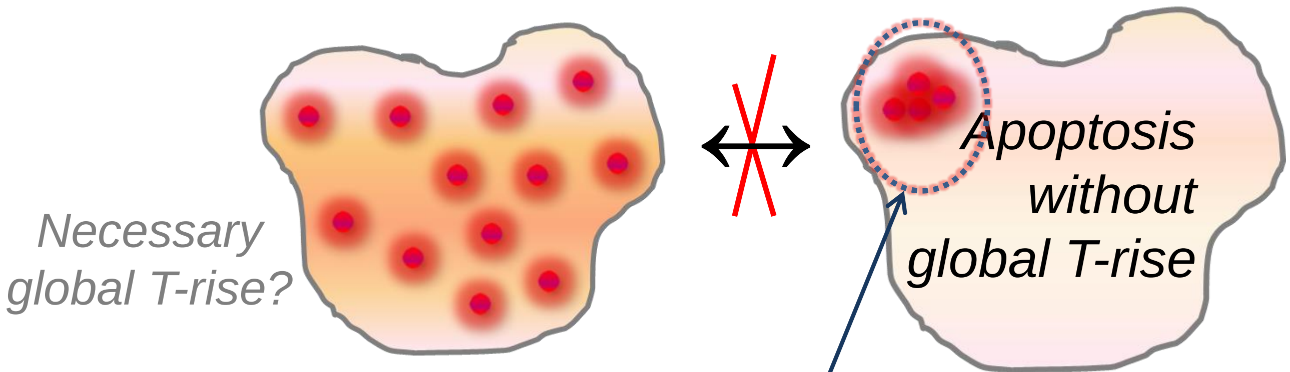
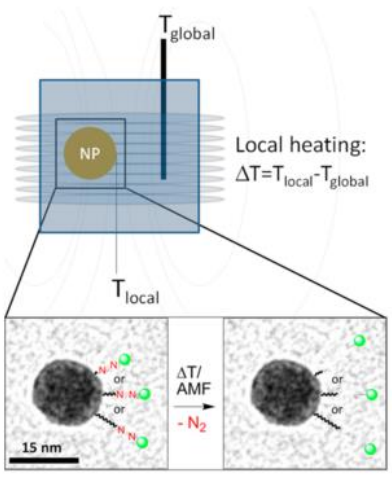
death is triggered even though the temperature increase in the cell culture during the hyperthermia treatment is lower than 0.5 °C.

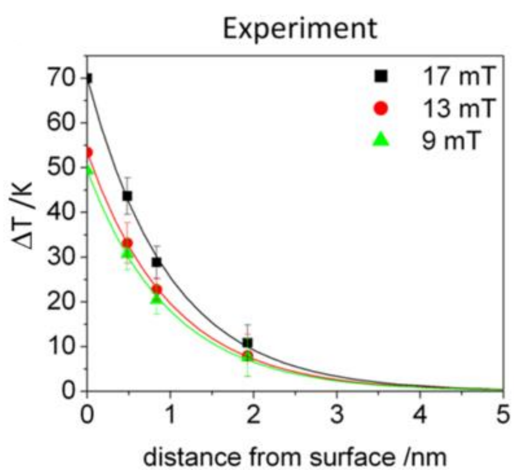
particle internalization in cells, or by the electromagnetic field on cells without nanoparticles. However, the application of an alternating electromagnetic field to cells incubated with this silica-coated manganese oxide induced significant cellular damage that finally lead to cell death by an apoptotic mechanism. Cell death is triggered even though the temperature increase in the cell culture during the hyperthermia treatment is lower than 0.5 °C.

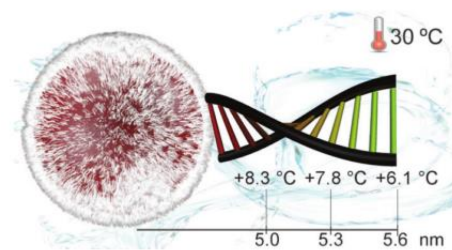
Motivation



Local heating enough to trigger cell death?





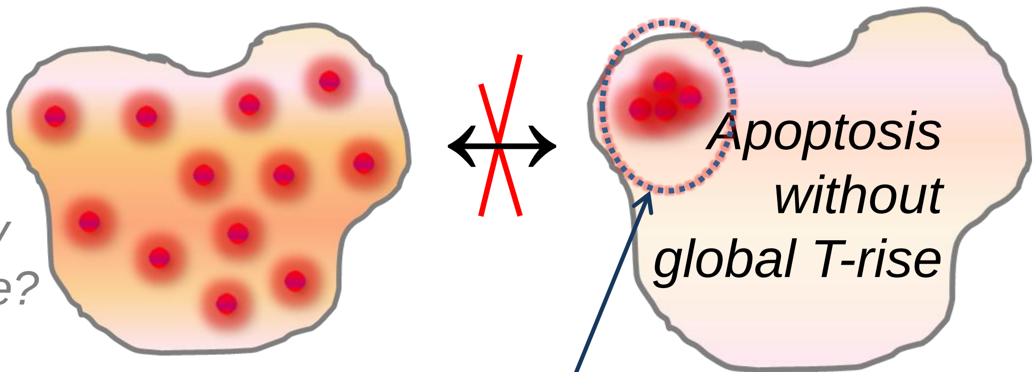


A. Riedinger, et. al., Nano Lett., 2013, 13, 2399–2406

J. T. Dias, et. al., Angew. Chem., 2013, 52, 11526–11529

Motivation

Necessary global T-rise?

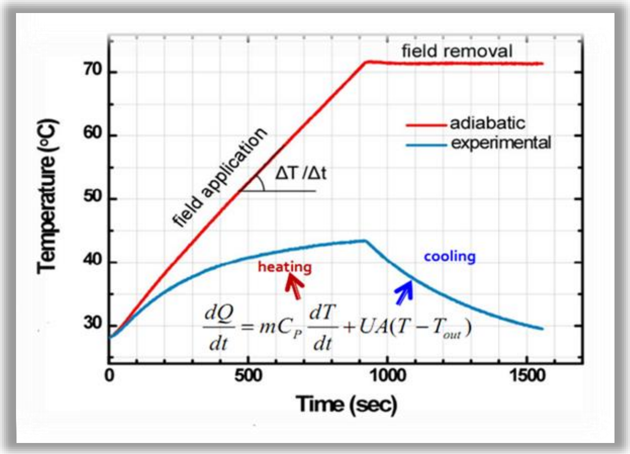


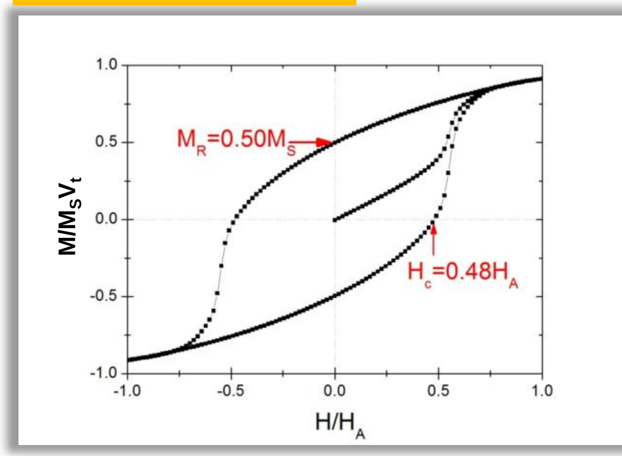
Local heating enough to trigger cell death?

~~Correlation sought through global SAR~~

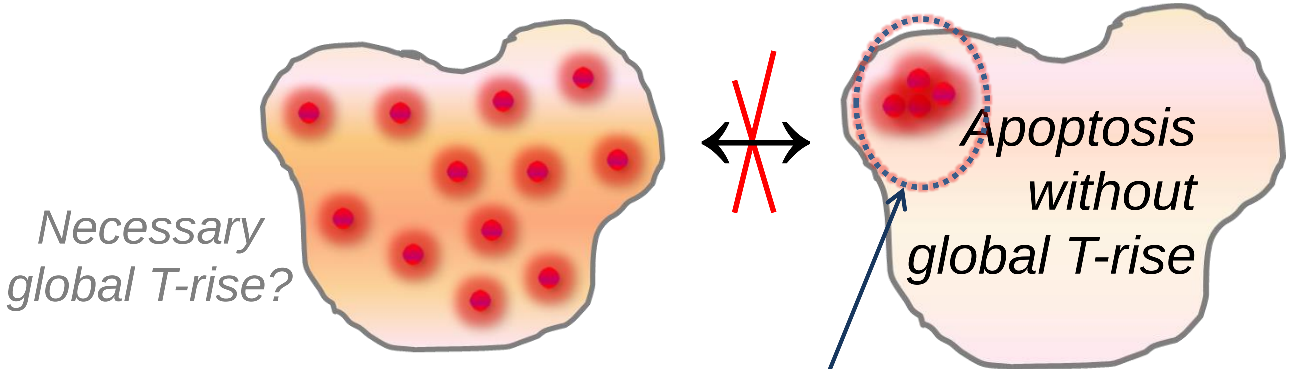
Global

Experiment: SAR= $c_p \Delta T/\Delta t$ $\not\leftrightarrow$ Theory: SAR= $HL\cdot f/V_t$





Motivation

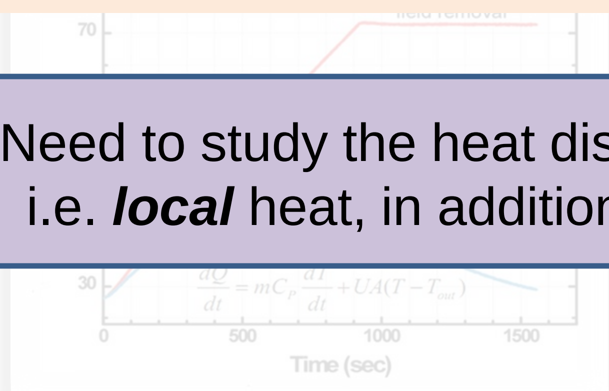


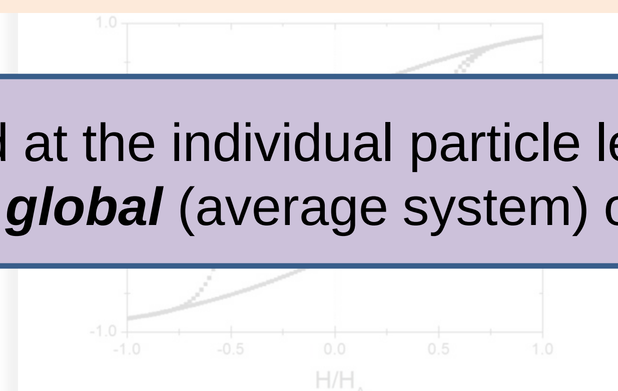
Local heating enough to trigger cell death?

Experiment:

Theory:

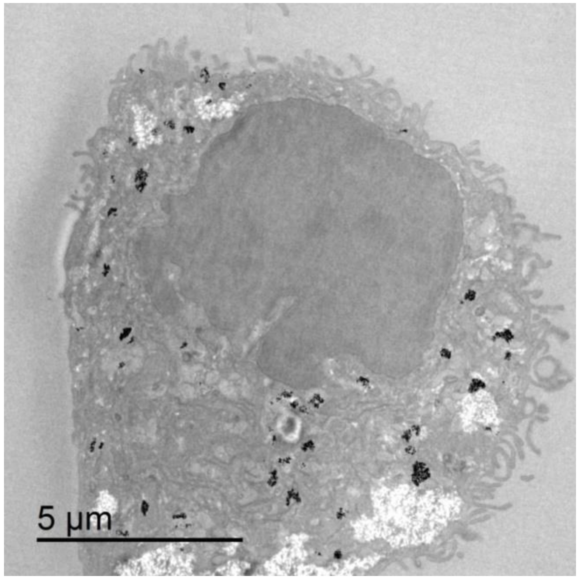
Need to build nm-scale time-resolved temperature profiles – requisite:
accurate knowledge of the power dissipated by each particle within the sysem





Need to study the heat dissipated at the individual particle level, i.e. ***local*** heat, in addition to the ***global*** (average system) one

kinetic Monte Carlo



L. Gutiérrez, M. P. Morales

- Aggregation after cell internalization → strong interparticle dipolar interactions

kinetic Monte Carlo (kMC) ideally suited

"cellular internalisation can disable Brownian relaxation"

ARTICLE

In Situ Measurement of Magnetization Relaxation of Internalized Nanoparticles in Live Cells

Dalibor Soukup,[†] Sandhya Moise,[†] Eva Céspedes,[†,‡] Jon Dobson,[§] and Neil D. Telling*[,†]

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Biomaterials 35 (2014) 6400–6411

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ELSEVIER

Magnetic hyperthermia efficiency in the cellular environment for different nanoparticle designs

CrossMark

Riccardo Di Corato [a], Ana Espinosa [a], Lenaic Lartigue [a], Mickael Tharaud [b], Sophie Chat [c], Teresa Pellegrino [d], Christine Ménager [e], Florence Gazeau [a], Claire Wilhelm [a,*]

[a] Laboratoire Matière et Systèmes Complexes, UMR 7057, CNRS and Université Paris Diderot, 75205 Paris Cedex 13, France
[b] Institut de Physique du Globe de Paris, UMR 7154, CNRS and Université Paris Diderot, 75205 Paris Cedex 13 France
[c] INRA, UR1196 GPL, MIMA2- Plateau de Microscopie Electronique 78352 Jouy-en-Josas, France
[d] Istituto Italiano di Tecnologia, I-16163 Genova, Italy
[e] Laboratoire Physicochimie des Electrolytes, Colloïdes et Sciences Analytiques PECSA UMR 7195, Université Pierre et Marie Curie UPMC-CNRS, 75252 Paris Cedex 05, France

kinetic Monte Carlo model

$$\frac{dP_1}{dt} = -W_{12}P_1 + W_{21}P_2$$

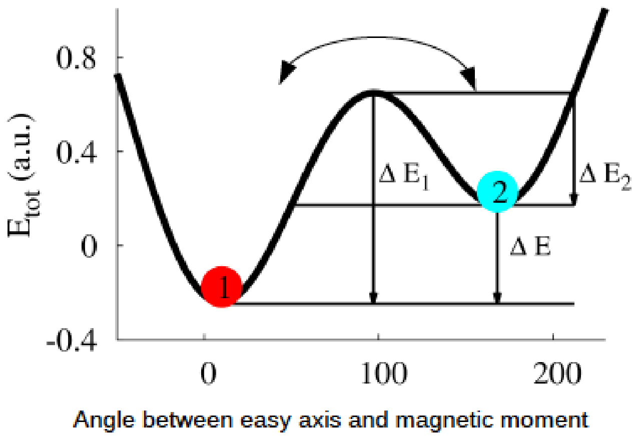
$$\frac{dP_2}{dt} = -W_{21}P_2 + W_{12}P_1$$

$$\tau = \frac{1}{(W_{12}+W_{21})} \qquad P_1 + P_2 = 1$$

$$\frac{dP_1}{dt} = \frac{1}{\tau}\left(W_{21}\tau - P_1\right)$$

$$\boldsymbol{\frac{dM(t)}{dt} = \frac{1}{\tau}\left(M_0(t) - M(t)\right)}$$

$$W_{12}, W_{21} = f_0 e^{\frac{-\Delta E_{1,2}}{K_B T}}$$



Master equation – real time description of the system dynamics

Models used here

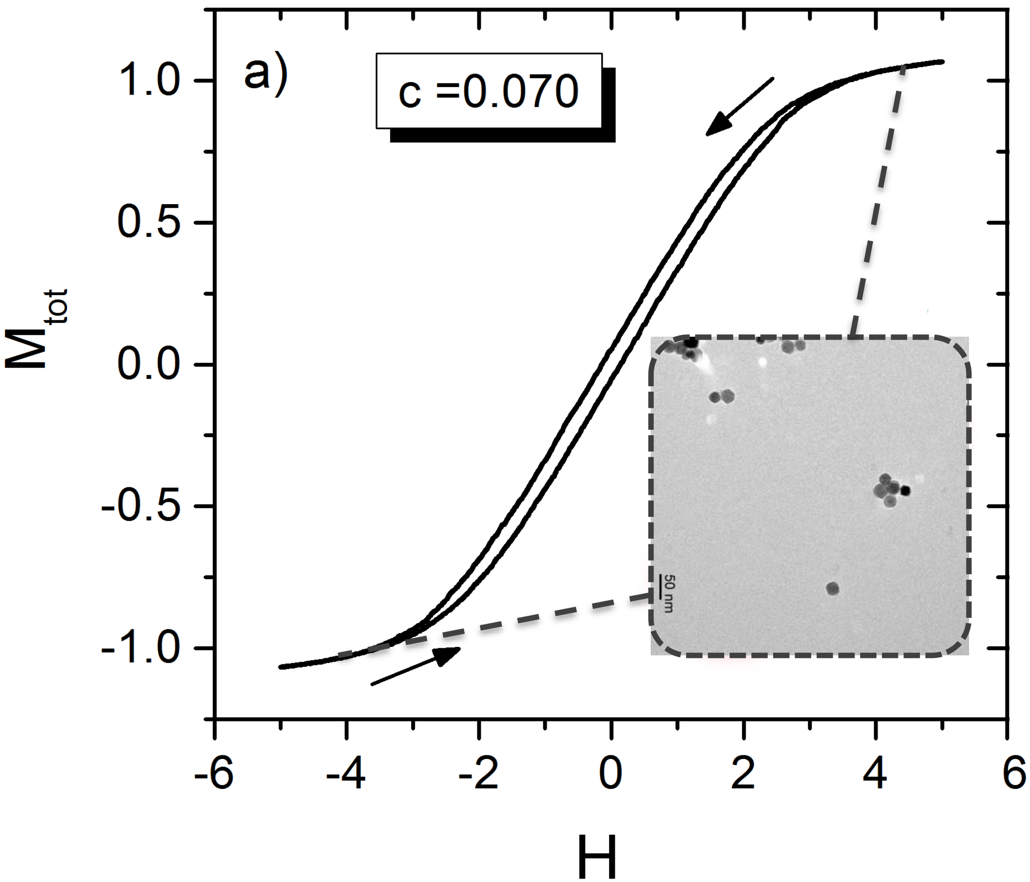
- Energy minimisation approach (KL)
- kMC model ***at zero K*** – equivalent to energy minisation.
- Both models used in parallel for tests – show heating for non-switching particles
- Direct estimate of temperature rise shows heating from precession

PHYSICAL REVIEW B **94**, 014[illegible]9 (2016)

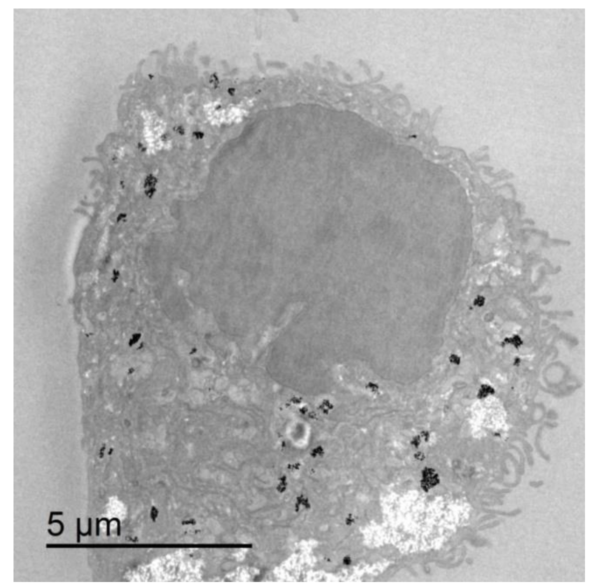
Self-consistent description of spin-phonon dynamics in ferromagnets

P. Nieves,[1,2] D. Serantes,[3,4] and O. Chubykalo-Fesenko[2]

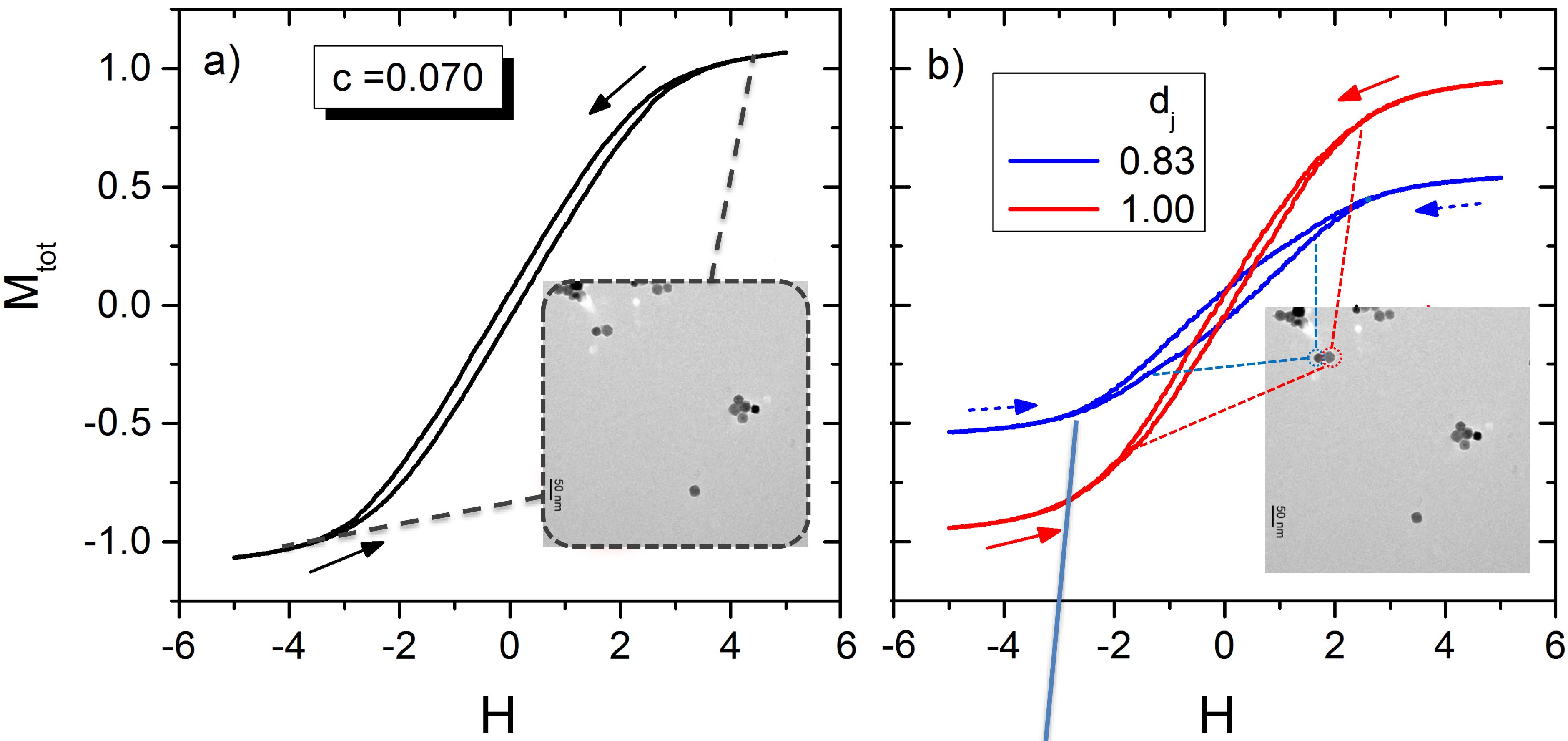
How to estimate the local heating?



$$SAR = HL \cdot f$$



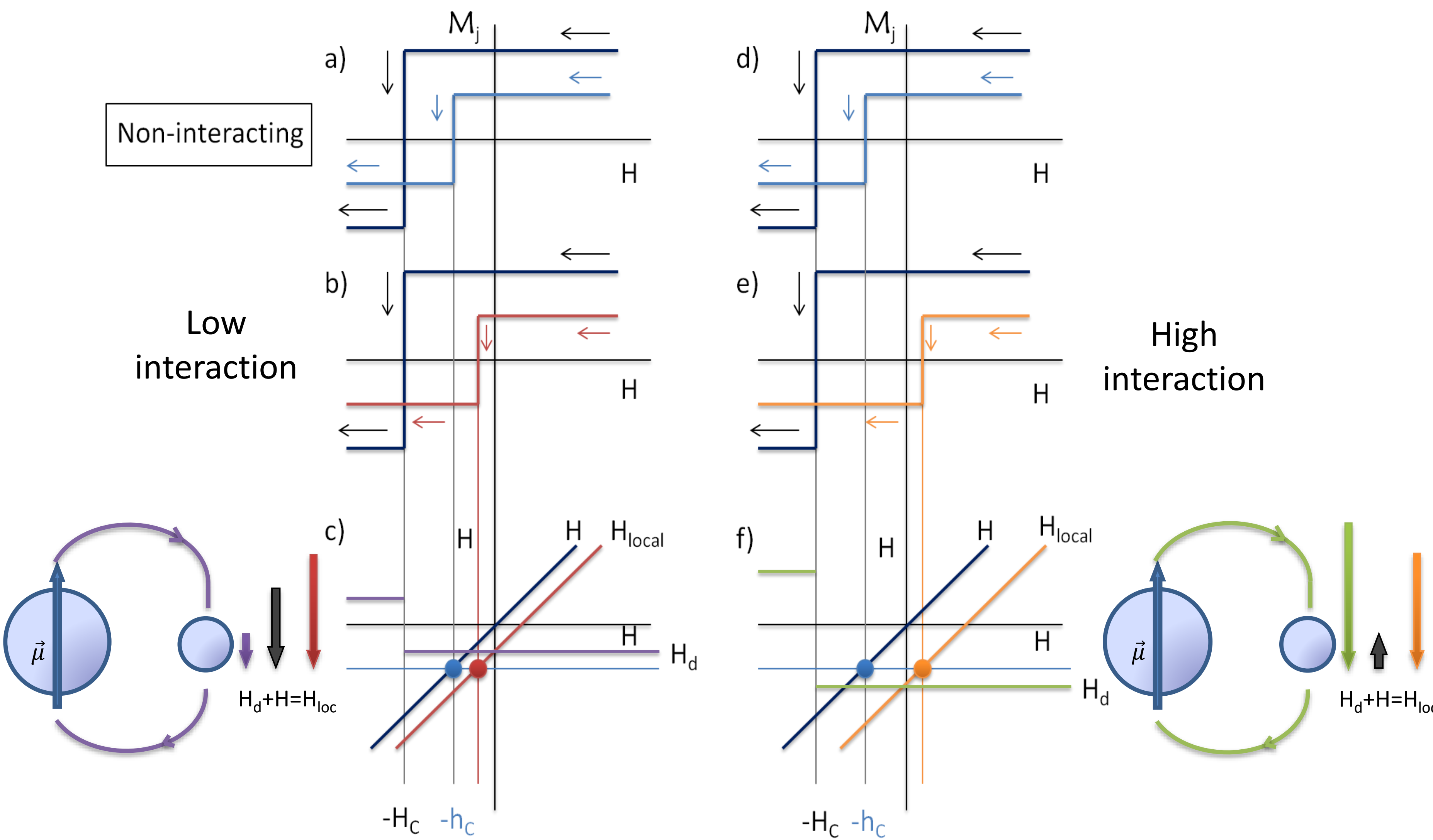
How to estimate the local heating?

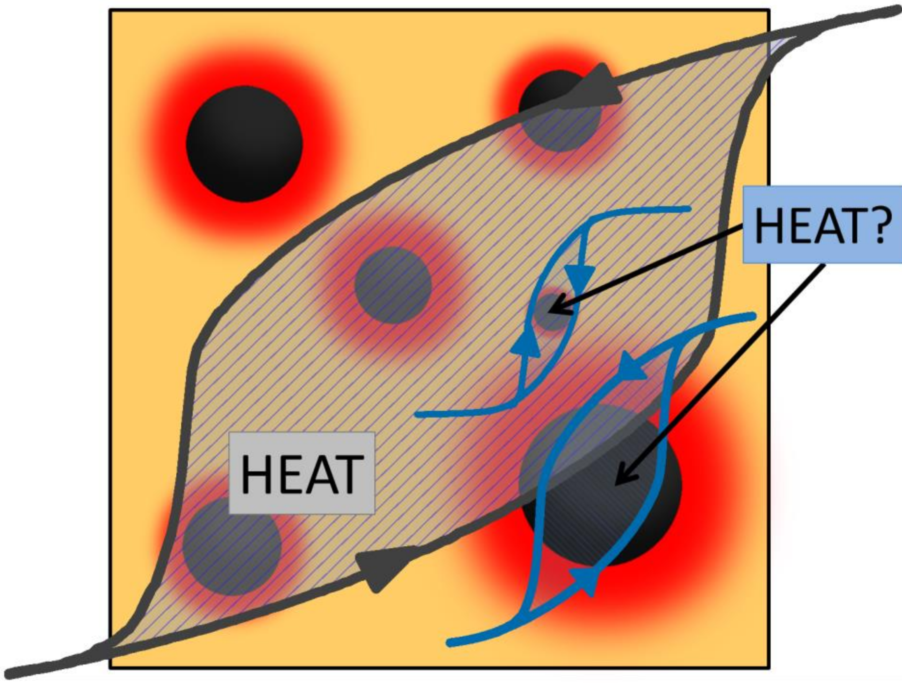


Inverted loops → "negative" area?

*Particles by L. Gutiérrez, M. P. Morales

2 particle case H_{dip} modifies H_{loc}: $\vec{\mu}_{small}$ flips if $|H_{loc}| > |H_C|$ (Aligned case)





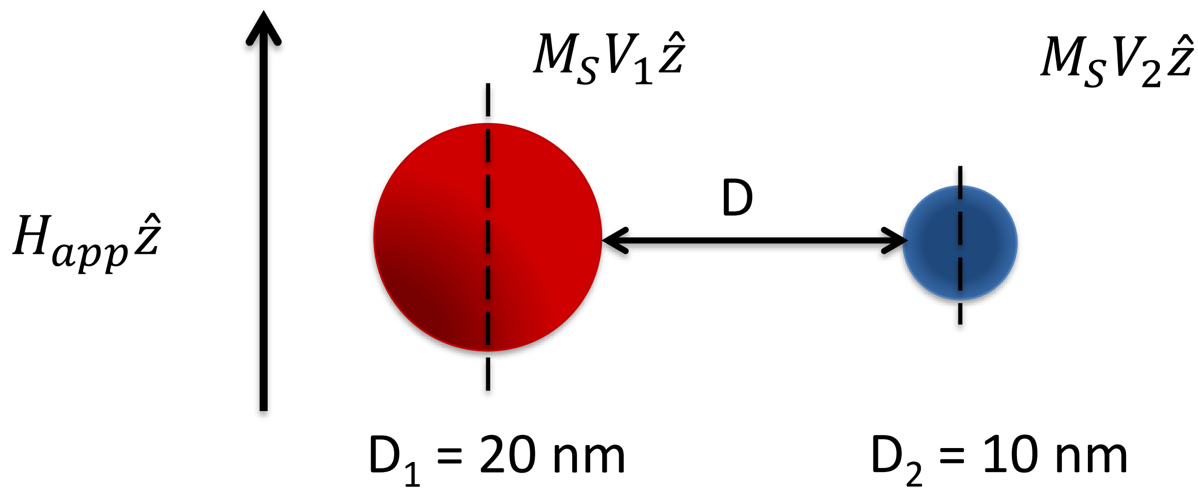
Premise:

Global area IS dissipated heat

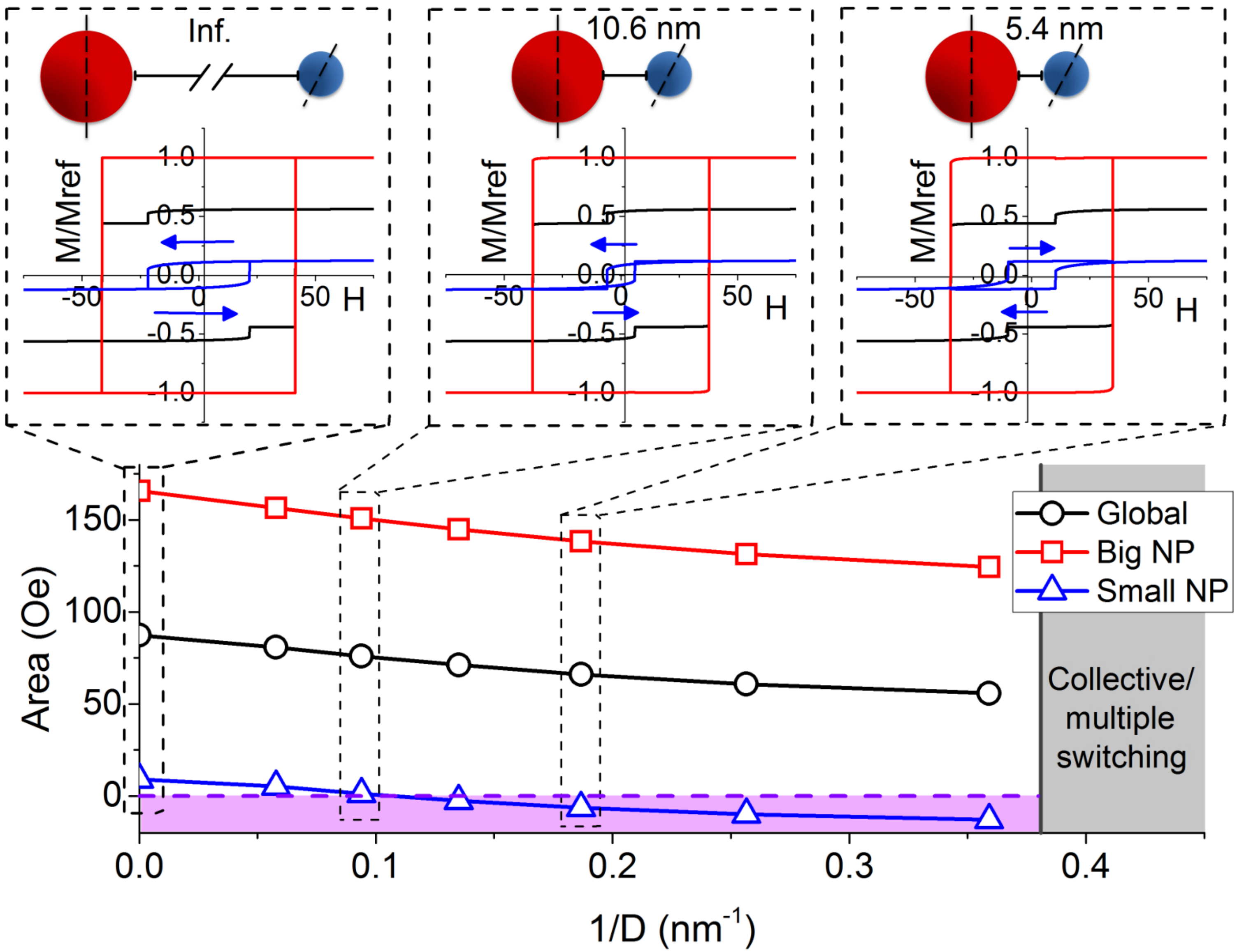
kMC

$E_T = E_K + E_Z + E_D$

Simple case:



Simulation of different interaction conditions – 2 particles



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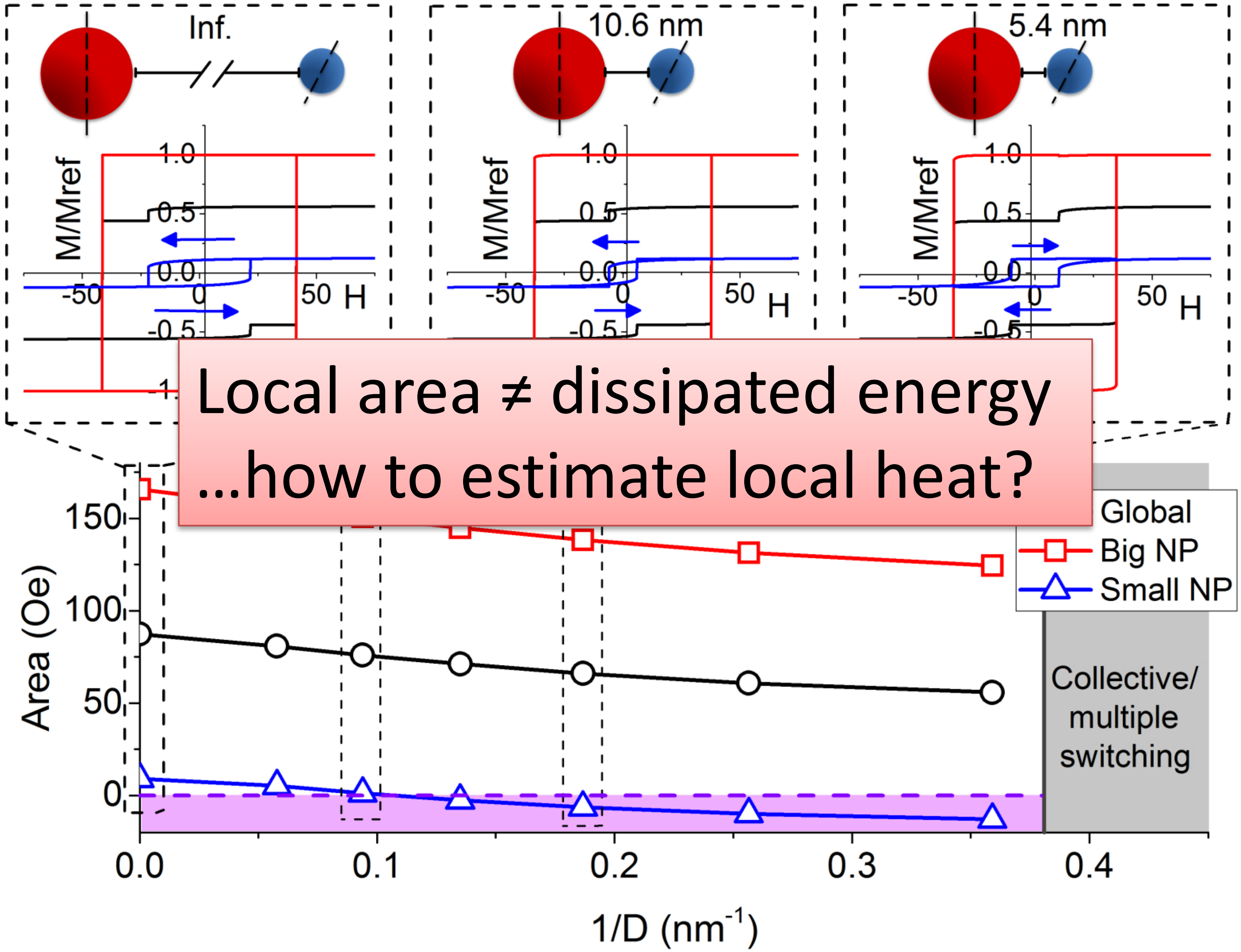
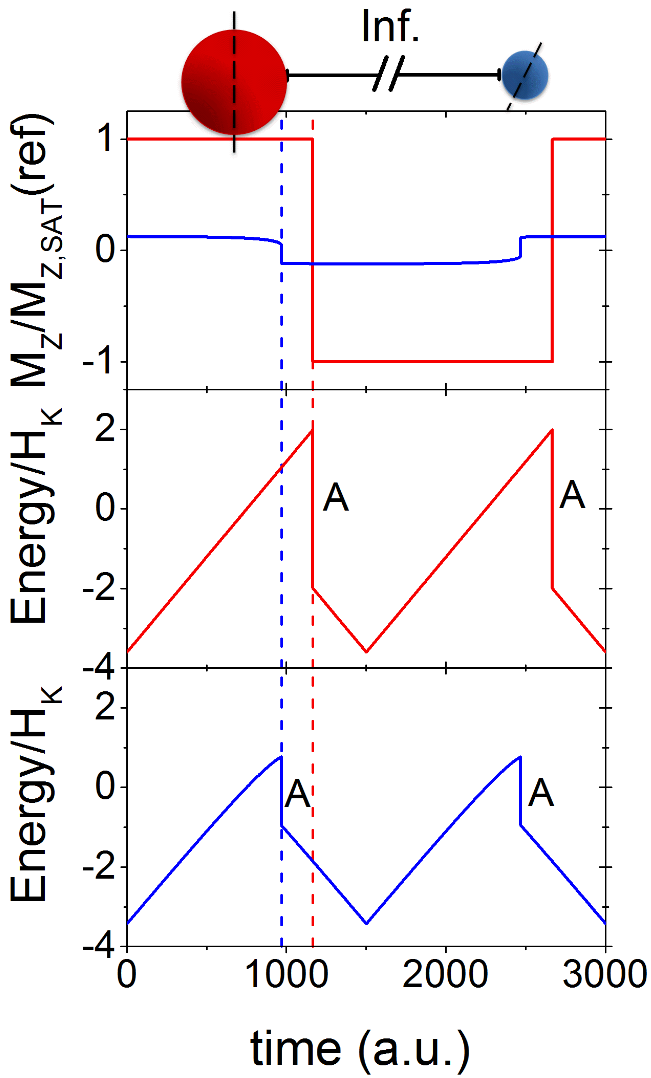
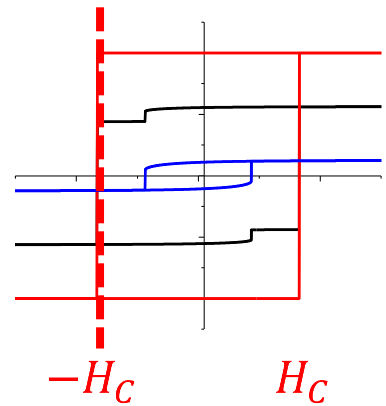


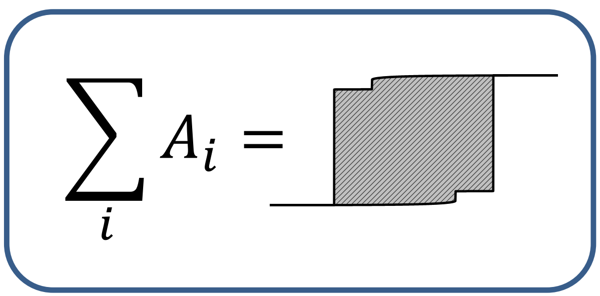
Local area ≠ dissipated energy

…how to estimate local heat?

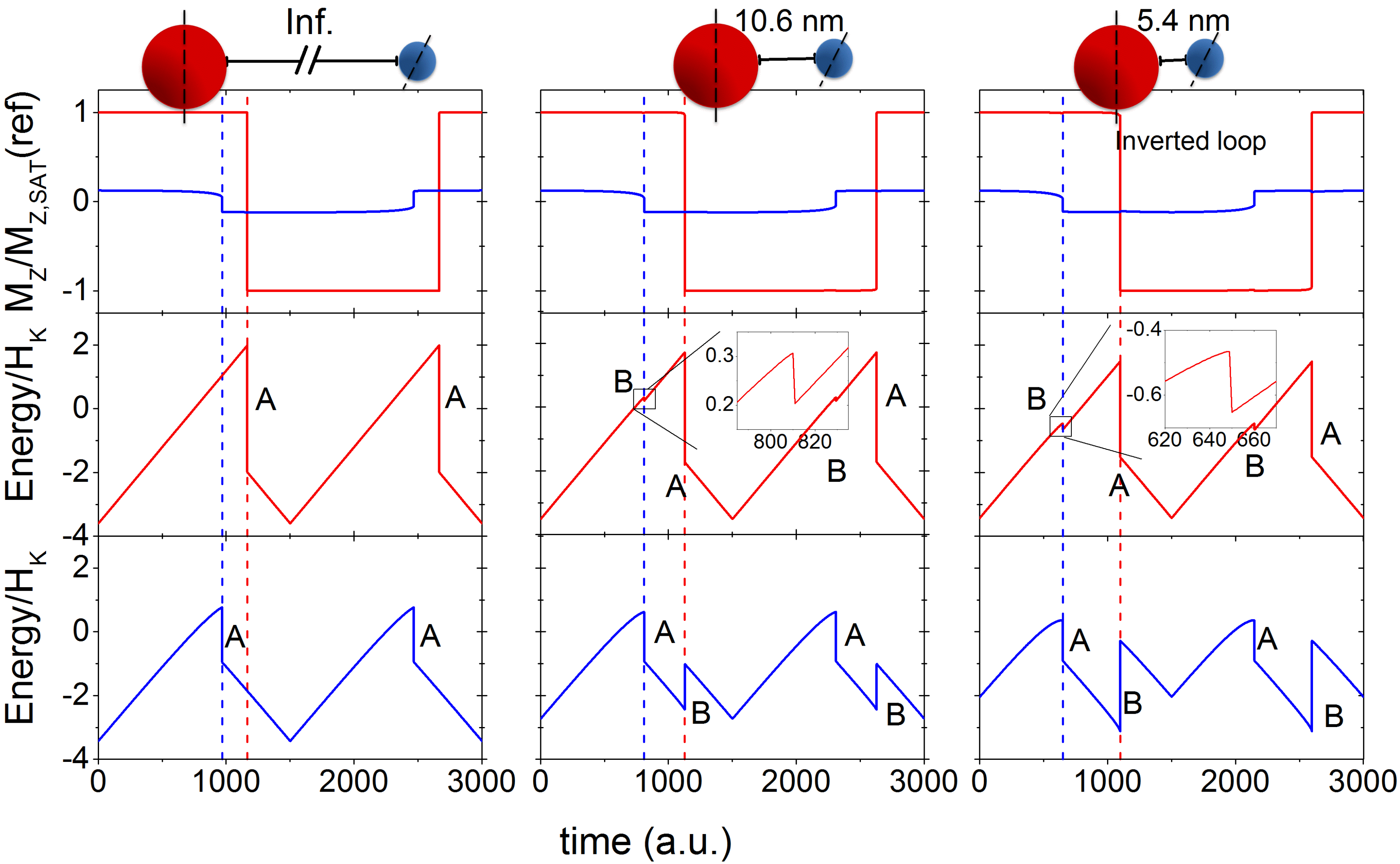
Evolution of each particle energy



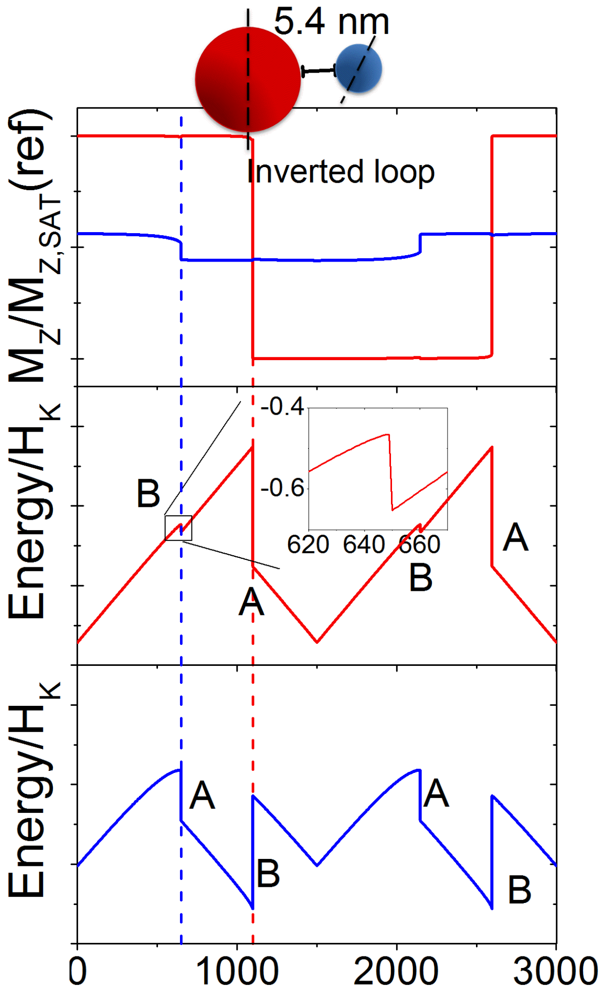




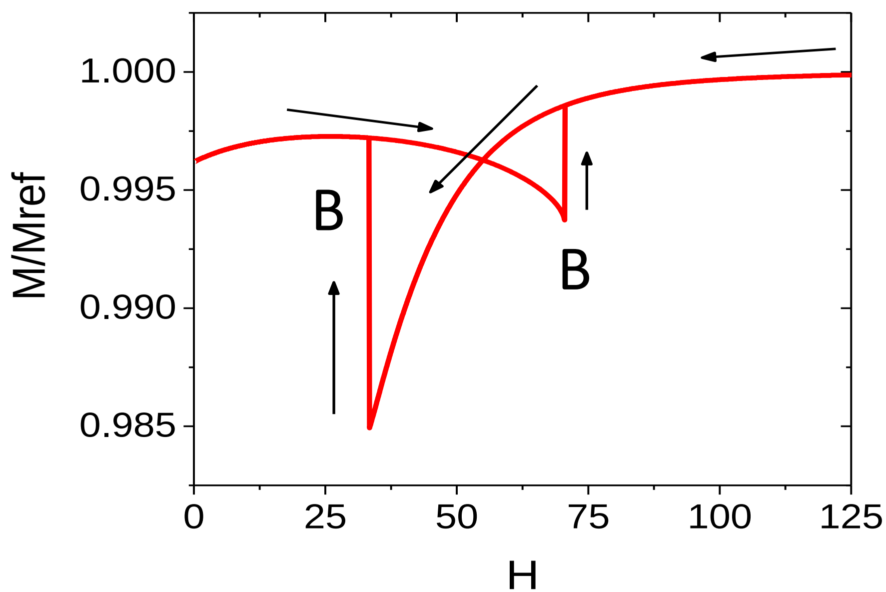
Evolution of each particle energy



Jump types



- A-type: irreversible transition between energy minima
- B-type: irreversible transition within a minimum caused by a jump of the neighboring particle



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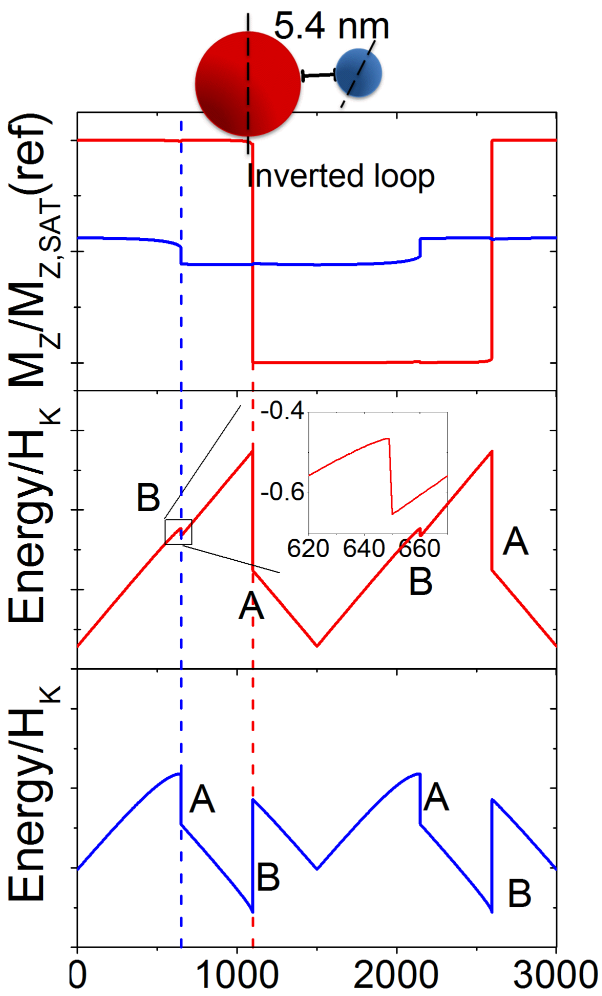

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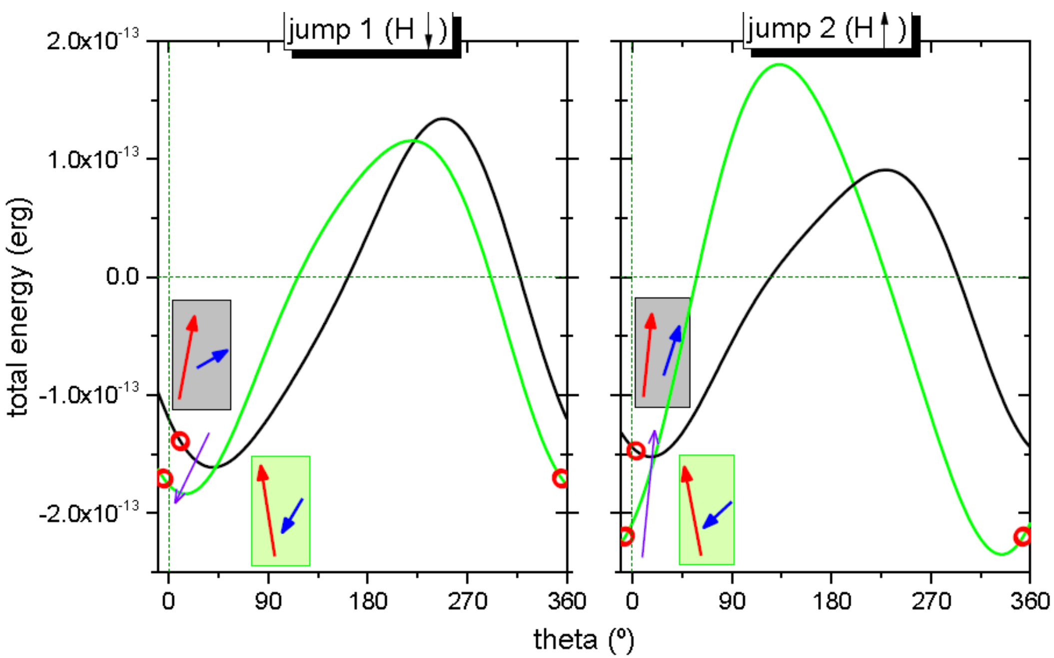
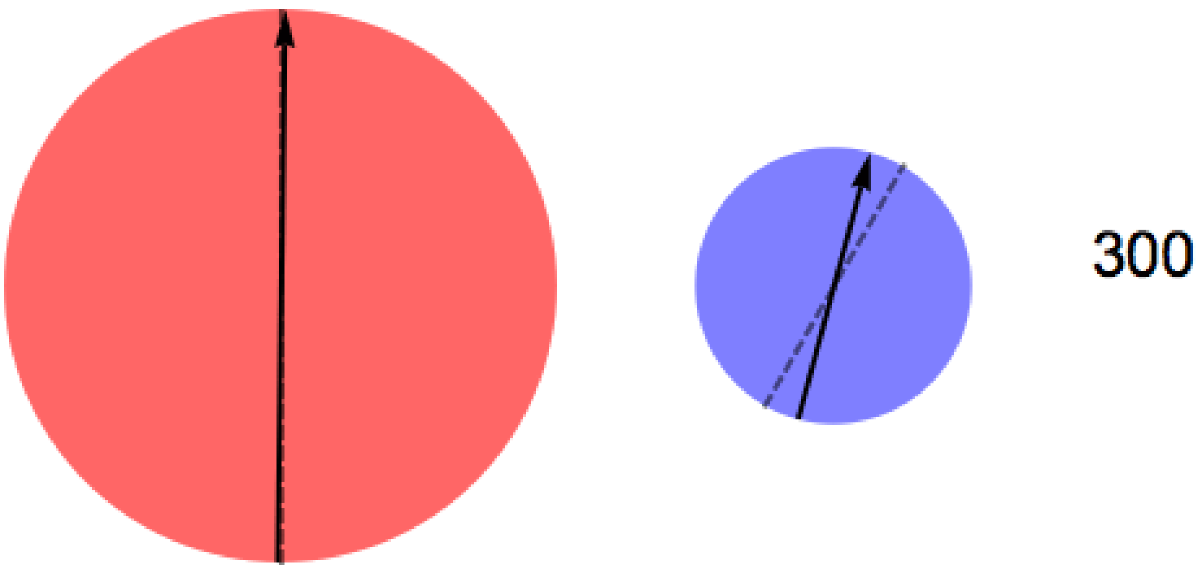
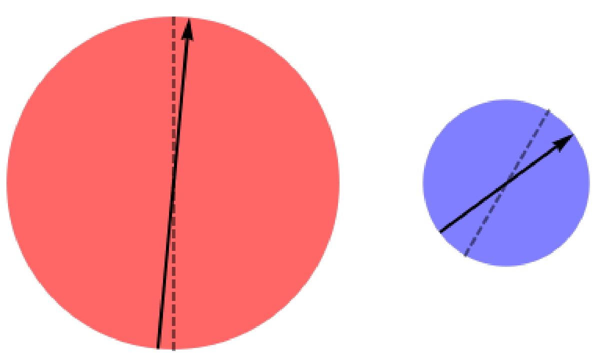


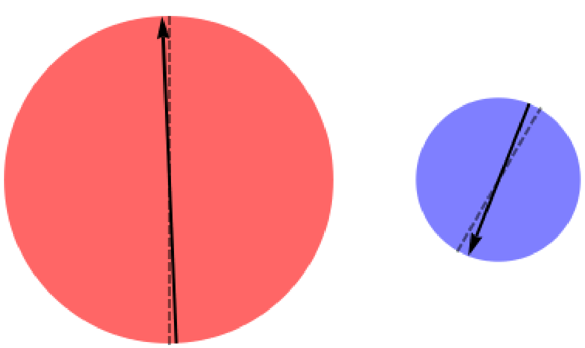
Defining jump types

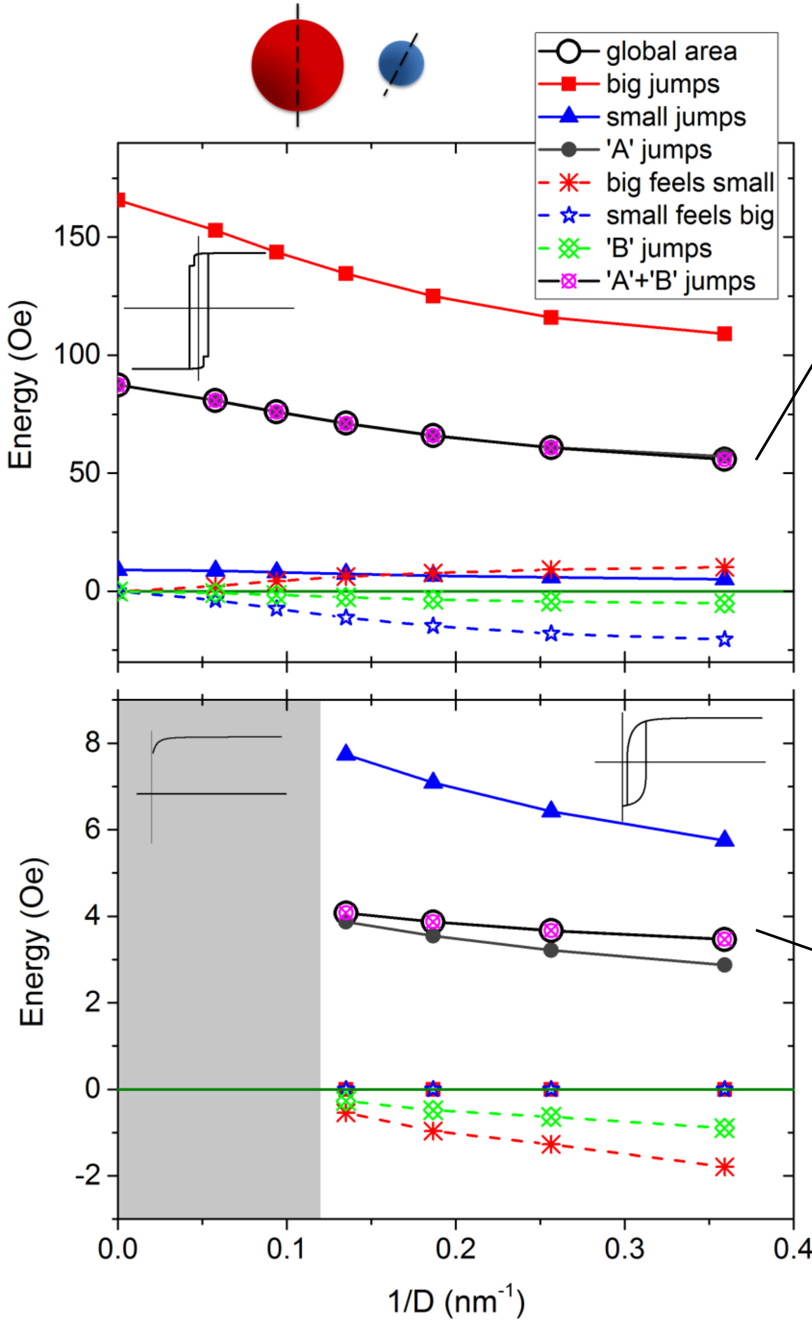


Before $\vec{\mu}_{small}$ switching:

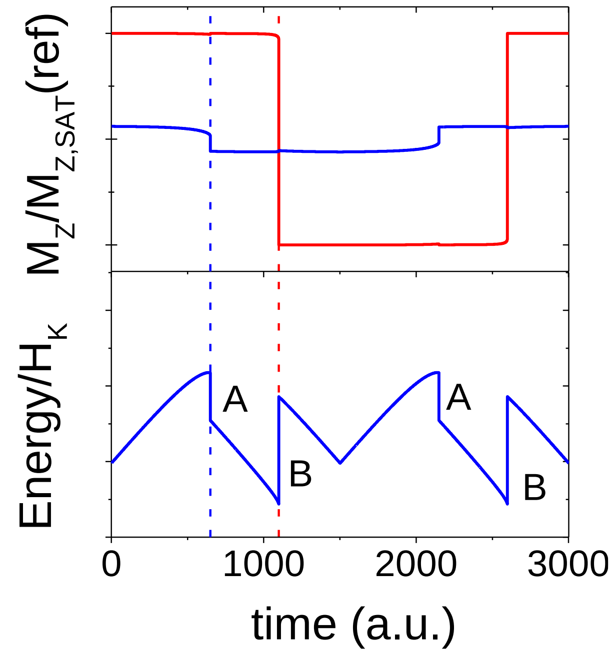


After $\vec{\mu}_{small}$ switching:





Global area is recovered from ‘A’ jumps and from ‘A’+’B’ jumps



Global area is only recovered from ‘A’+’B’ jumps

Direct ΔT estimation

PHYSICAL REVIEW B **94**, 014409 (2016)

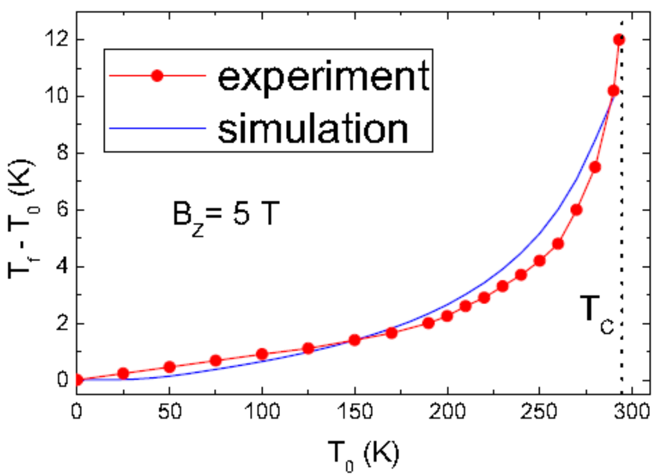
Self-consistent description of spin-phonon dynamics in ferromagnets

P. Nieves,[1,2] D. Serantes,[3,4] and O. Chubykalo-Fesenko[2]

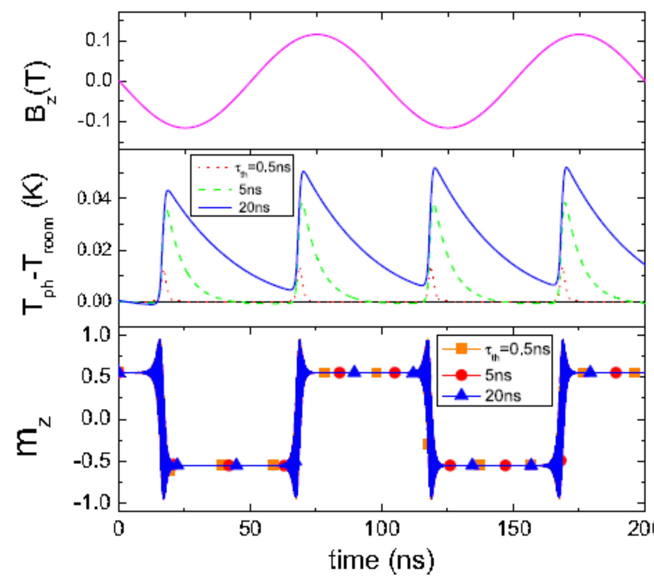
$$\begin{cases} \dfrac{d\mathbf{m}}{dt} = -\gamma \mathbf{m} \times \mathbf{H}_{\text{eff}} + \gamma \alpha_{\parallel} \dfrac{\mathbf{m} \cdot \mathbf{H}_{\text{eff}}}{m^2} \mathbf{m} - \gamma \alpha_{\perp} \dfrac{\mathbf{m} \times (\mathbf{m} \times \mathbf{H}_{\text{eff}})}{m^2}, \\ \dfrac{dT_{ph}}{dt} = \dfrac{\gamma \alpha_{\parallel} M_s J_0}{C_{ph} \mu_{at}} \mathbf{m} \cdot \mathbf{H}_{\text{eff}} + \dfrac{\gamma \alpha'_{\perp} M_s}{C_{ph}} \dfrac{(\mathbf{m} \times \mathbf{h})^2}{m^2} \equiv f(\mathbf{m}, T_{ph}), \end{cases}$$

MFH

$$\tau_{\parallel} = \frac{\widetilde{\chi}_{\parallel}}{\gamma \alpha_{\parallel}},$$



$$\tau_{\perp} = \frac{m_e}{2\gamma h \alpha_{\perp}}$$



MCE

FIG. 1. Temperature change $\Delta T = T_f - T_0$ versus the initial temperature T_0 in Gd due to the application of an external magnetic field $B_z = \mu_0 H_z = 5$ T calculated using the qLLB equation [Eq. (5)] coupled to Eq. (15) (solid blue line) The dotted red line corresponds to the experiment from Ref. [33] (solid dots).

FIG. 4. The z component of the external applied magnetic field (upper panel), phonon bath temperature (middle panel), and z component of the magnetization (lower panel) dynamics in Fe_3O_4 calculated using the qLLB equation (5) coupled to Eq. (18) for different values of $\tau_{th} = 0.5$, 5, and 20 ns.

Direct ΔT estimation

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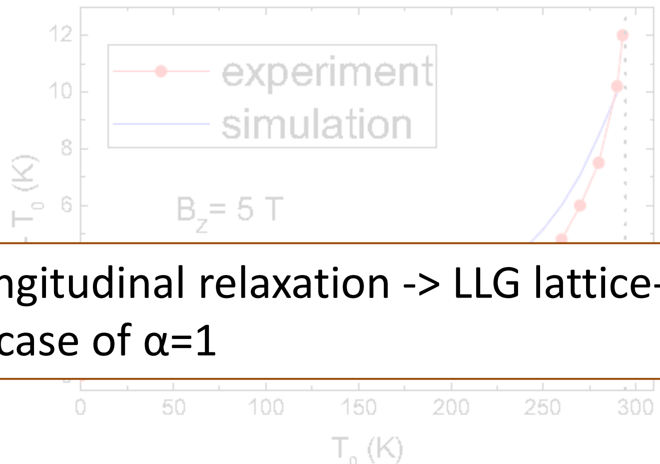
$$\tau_{\parallel} = \frac{\widetilde{\chi}_{\parallel}}{\gamma\alpha_{\parallel}},$$



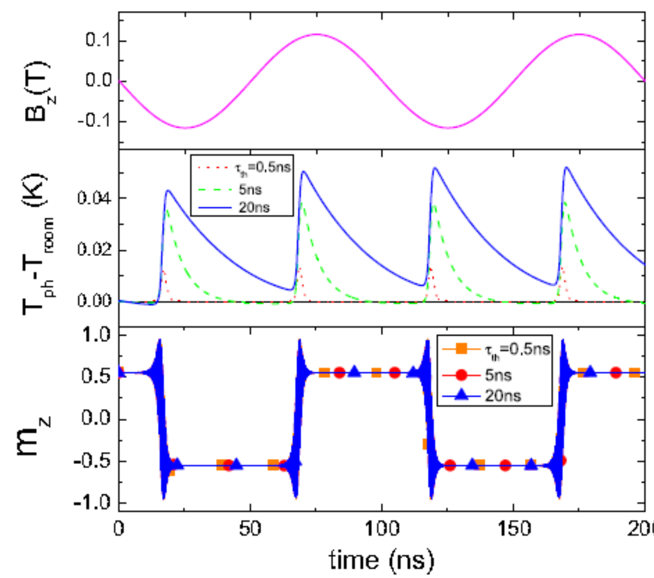
$$\tau_{\perp} = \frac{m_e}{2\gamma\hbar\alpha_{\perp}}$$

- No longitudinal relaxation -> LLG lattice-coupled
- Limit case of α=1

MCE

FIG. 1. Temperature change $\Delta T = T_f - T_0$ versus the initial temperature T_0 in Gd due to the application of an external magnetic field $B_z = \mu_0 H_z = 5$ T calculated using the qLLB equation [Eq. (5)] coupled to Eq. (15) (solid blue line) The dotted red line corresponds to the experiment from Ref. [33] (solid dots).

MFH



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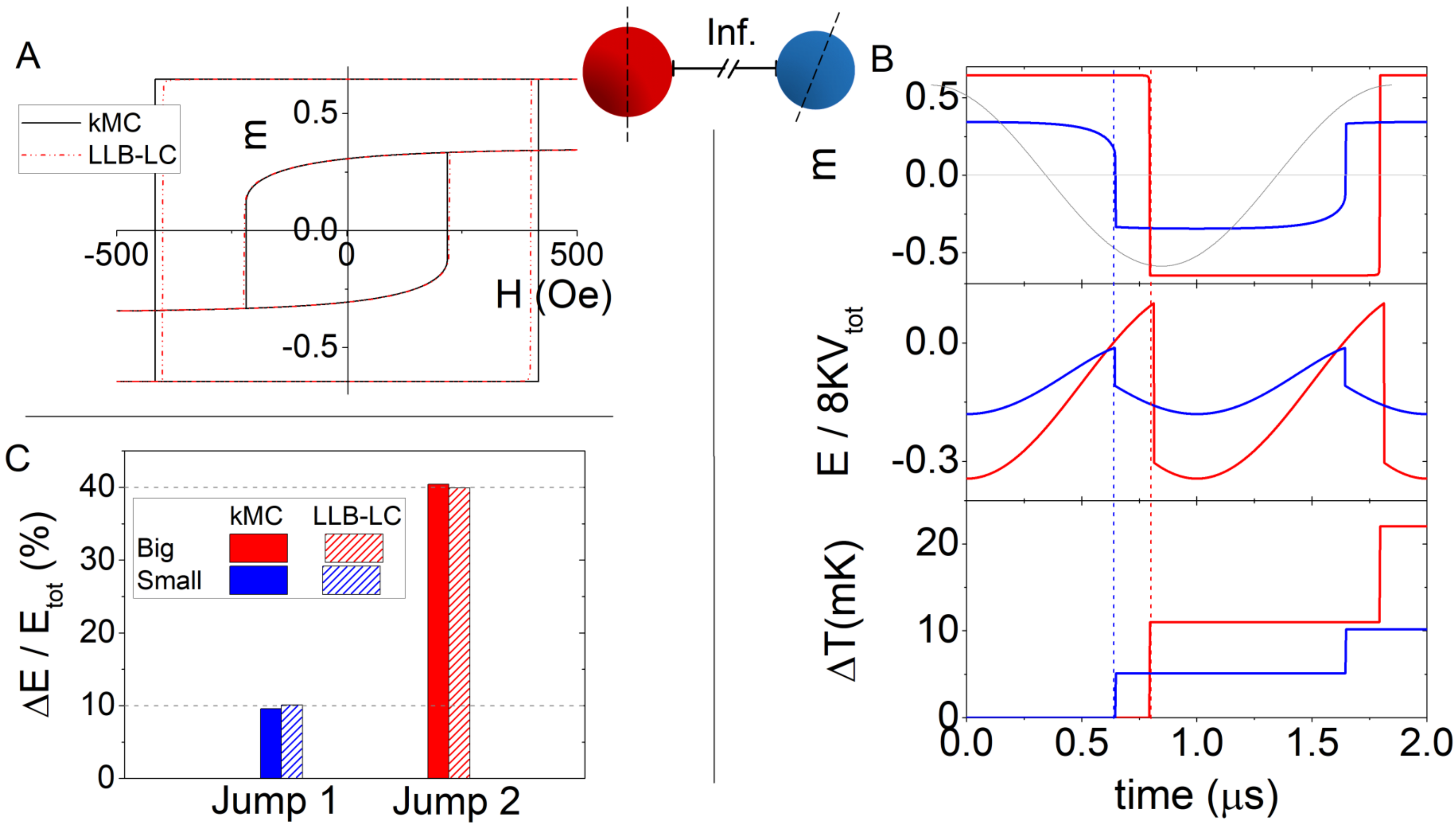
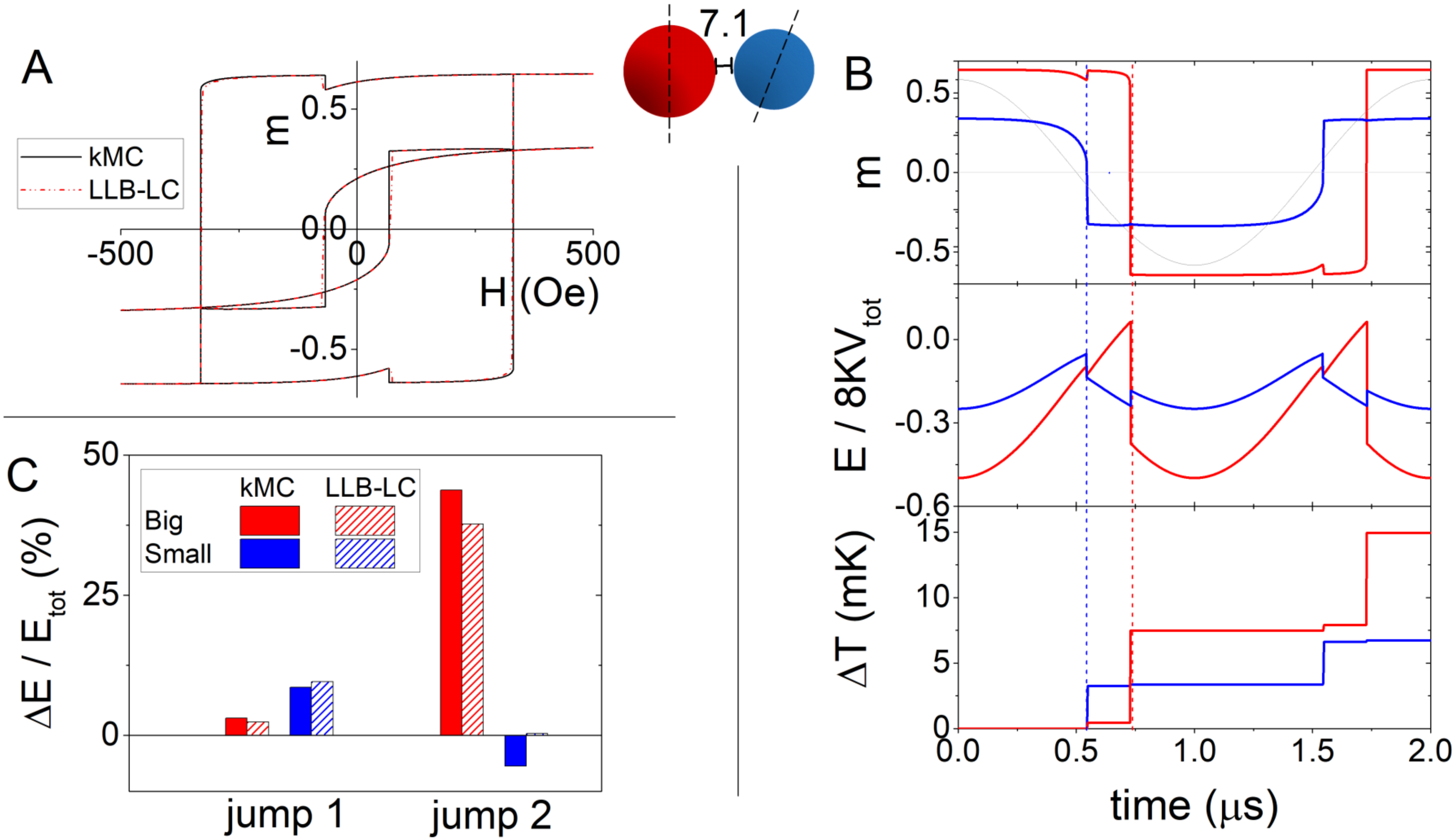
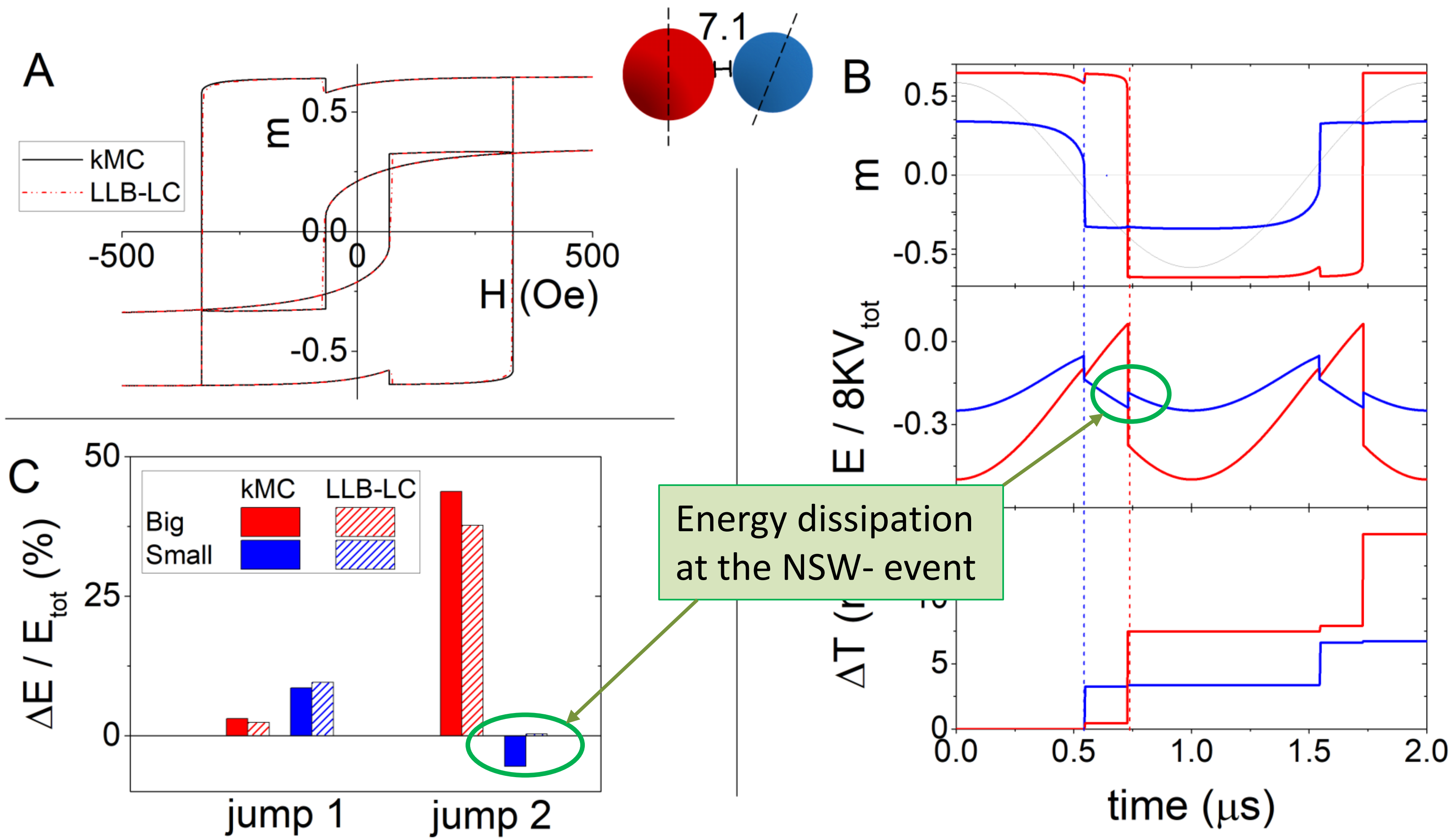
Direct ΔT estimation – noninteracting case



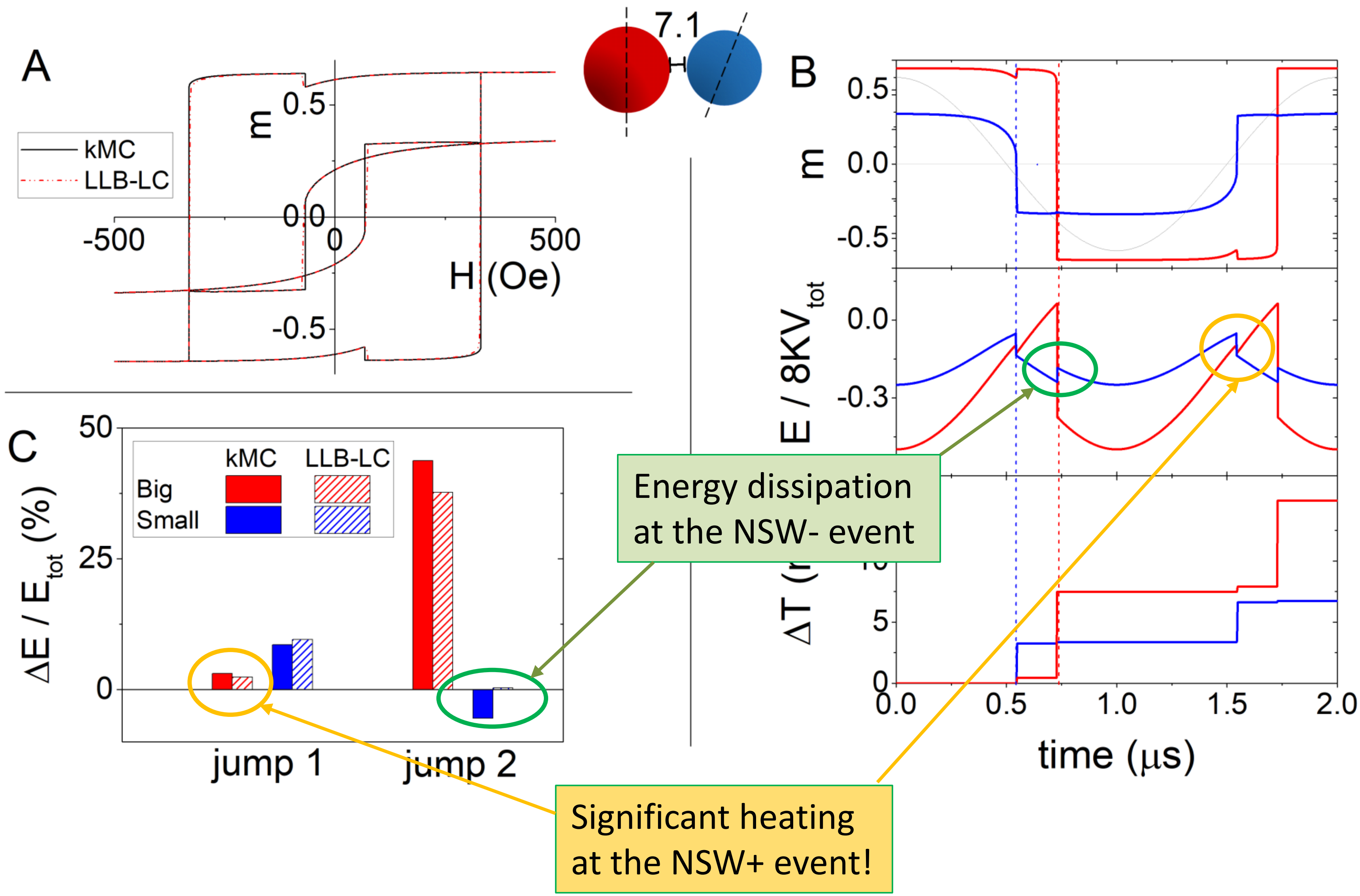
Direct ΔT estimation – interacting case



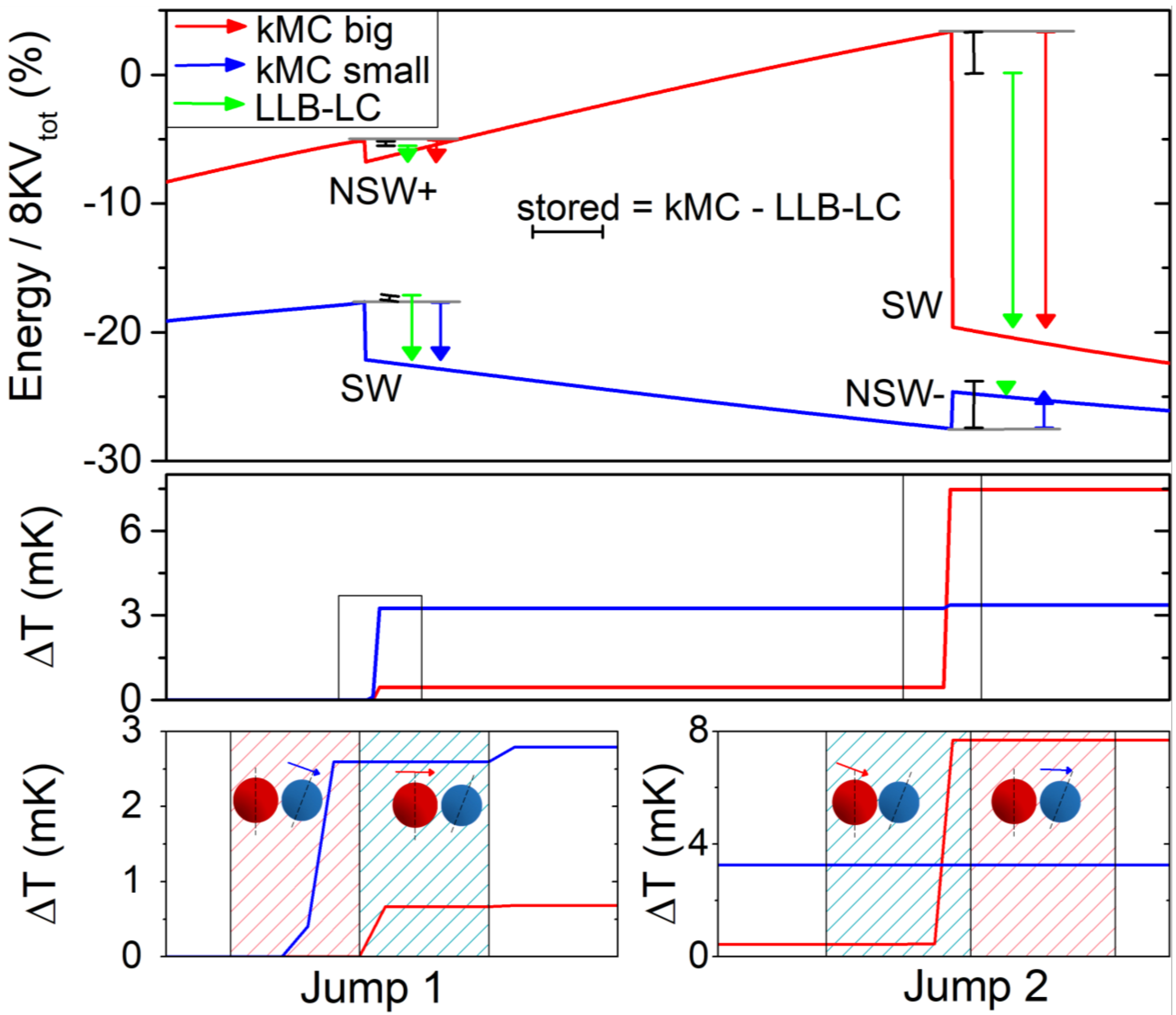
Direct ΔT estimation – interacting case



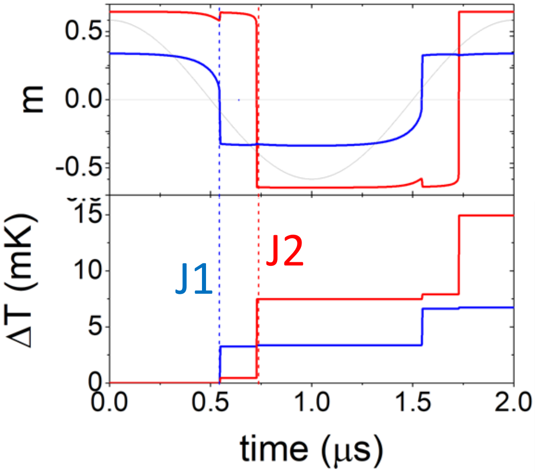
Direct ΔT estimation – interacting case



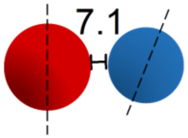
Direct ΔT estimation – interacting case

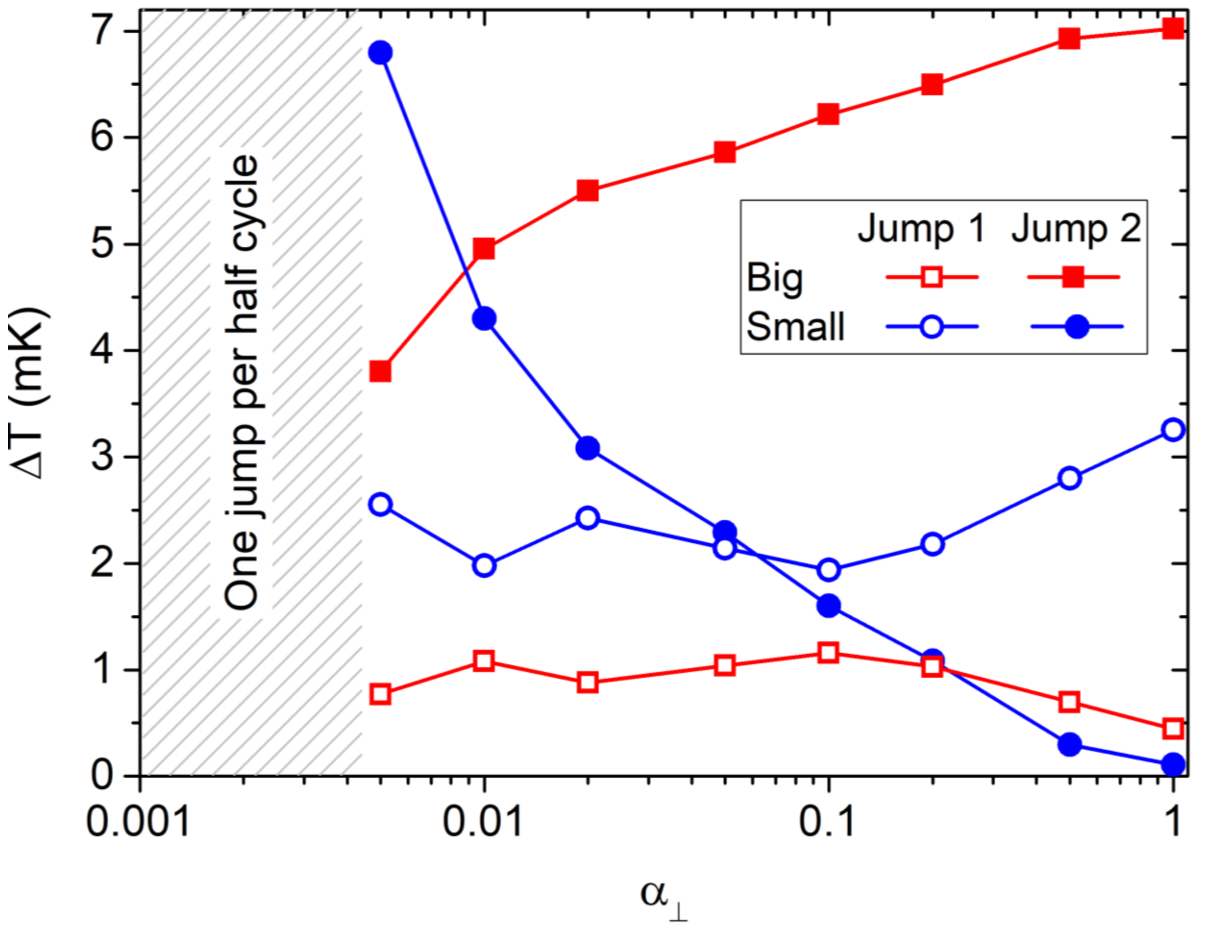


Direct ΔT estimation – interacting case

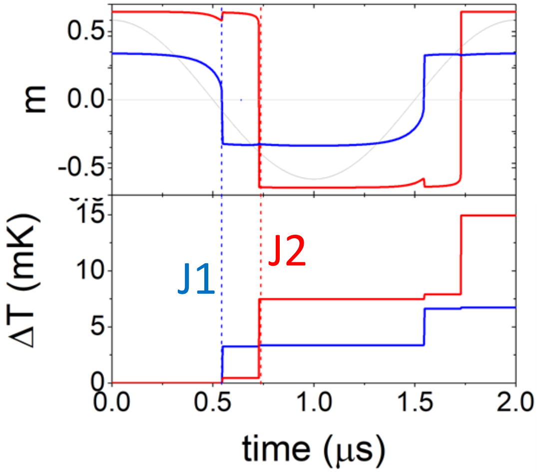


Dynamics

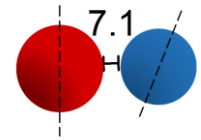


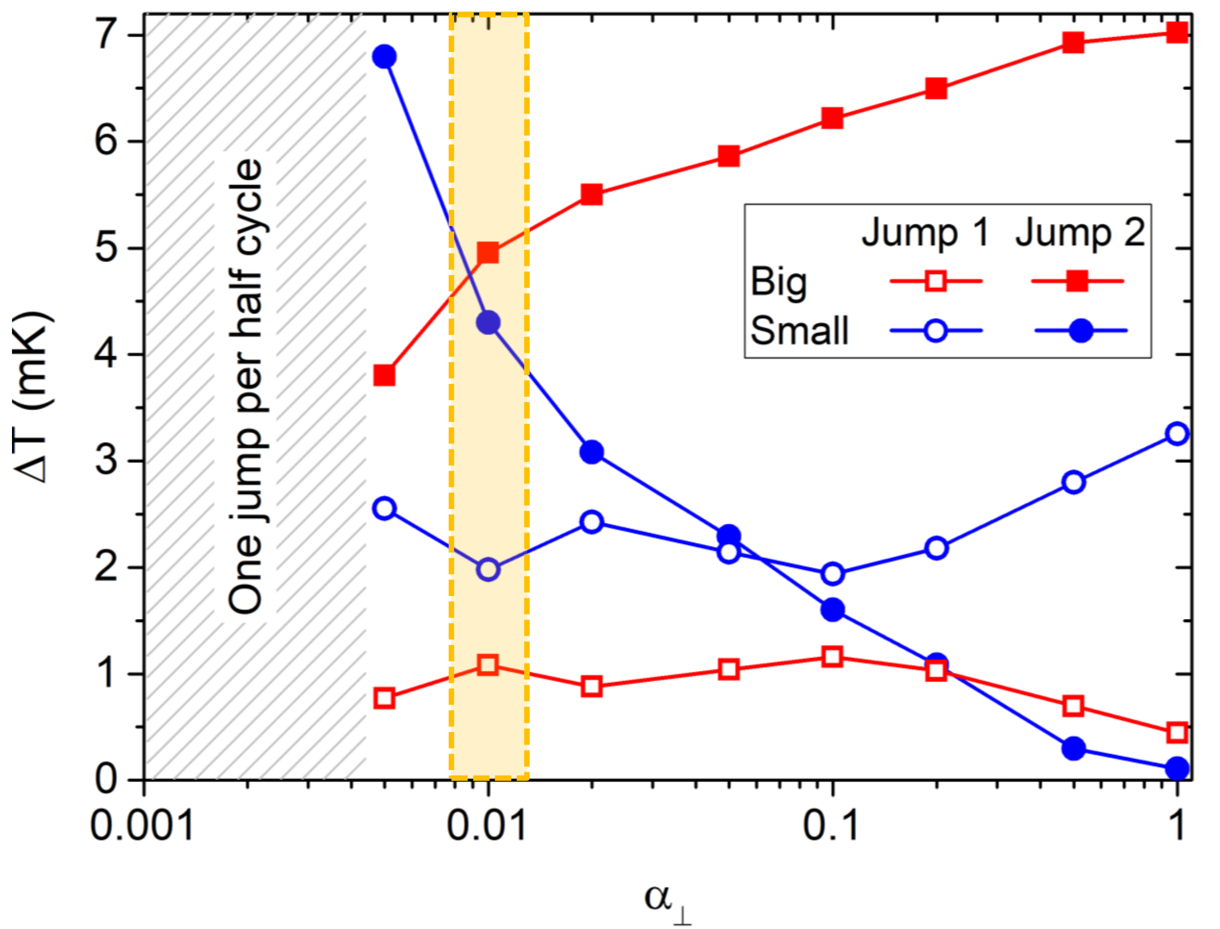


Direct ΔT estimation – interacting case

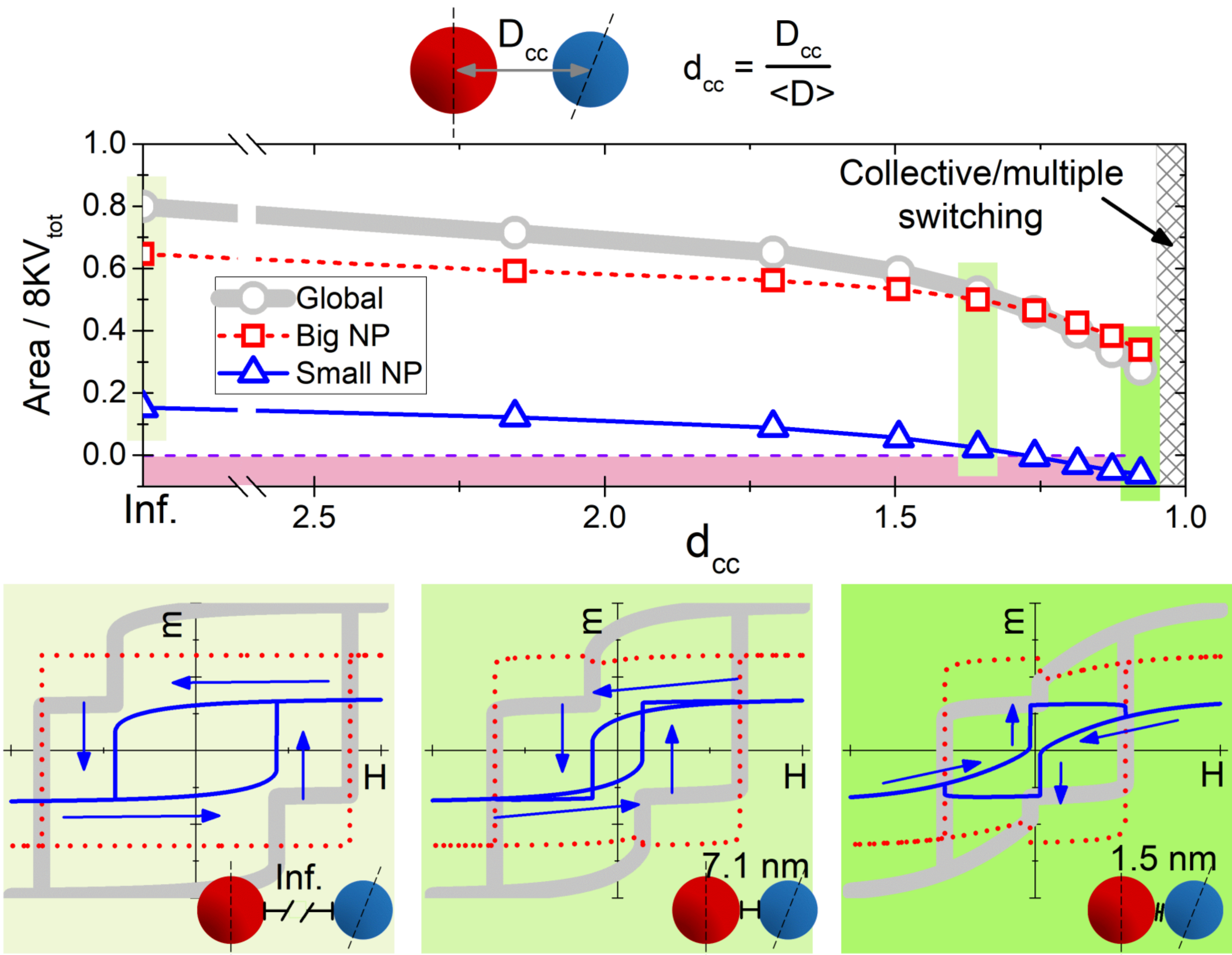


Dynamics





Direct ΔT estimation – interacting case

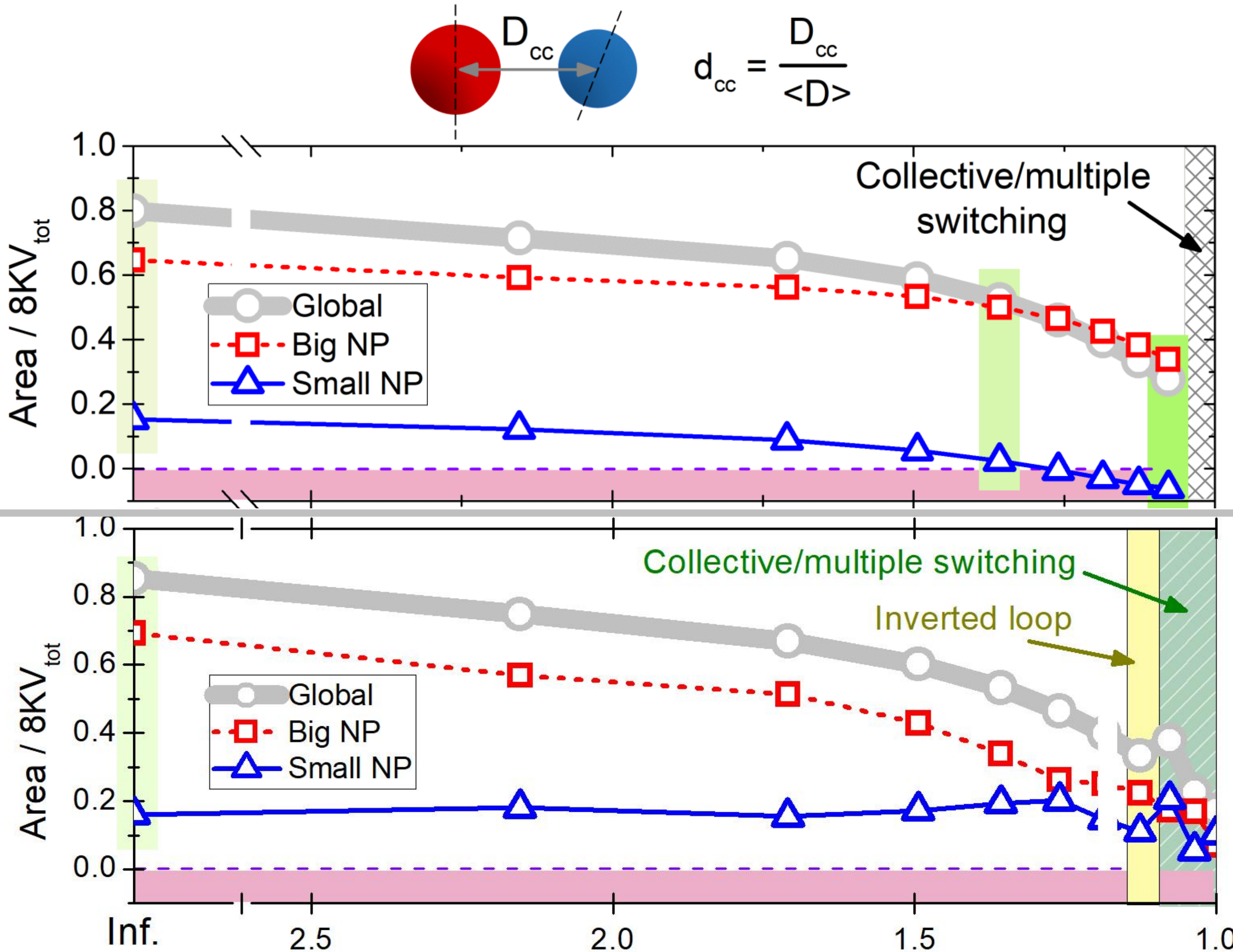


Direct ΔT estimation – interacting case

$$d_{cc} = \frac{D_{cc}}{\langle D \rangle}$$

Areas α=1.0

ΔT α=0.01



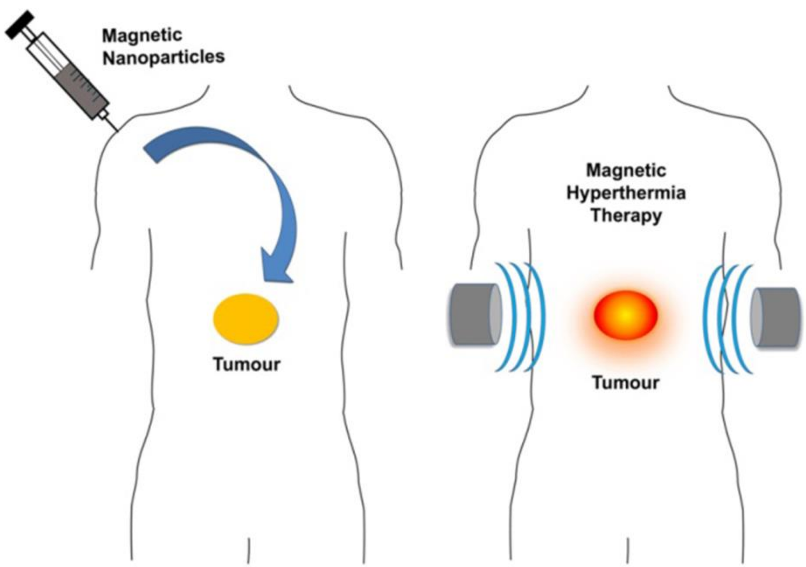
Very similar M(H) curves

Summary

- Experiments show the need to study *local* heating
- Local inverted hysteresis loops appear for strong interacting conditions
- Local areas do not account for local dissipated heat
- Energy jumps of individual NPs are a promising way to access local information
- Energy may be released also by the non-switching particle
- Third mechanism is dissipation during precessional switching
- Next steps
  - Develoment of kinetic Monte Carlo model to calculate local heat dissipation.
  - Coupled with bioheat equation to calculate local temperature rise for comparison with experiment
- Strong implications for other related areas such as heat-triggered drug release.

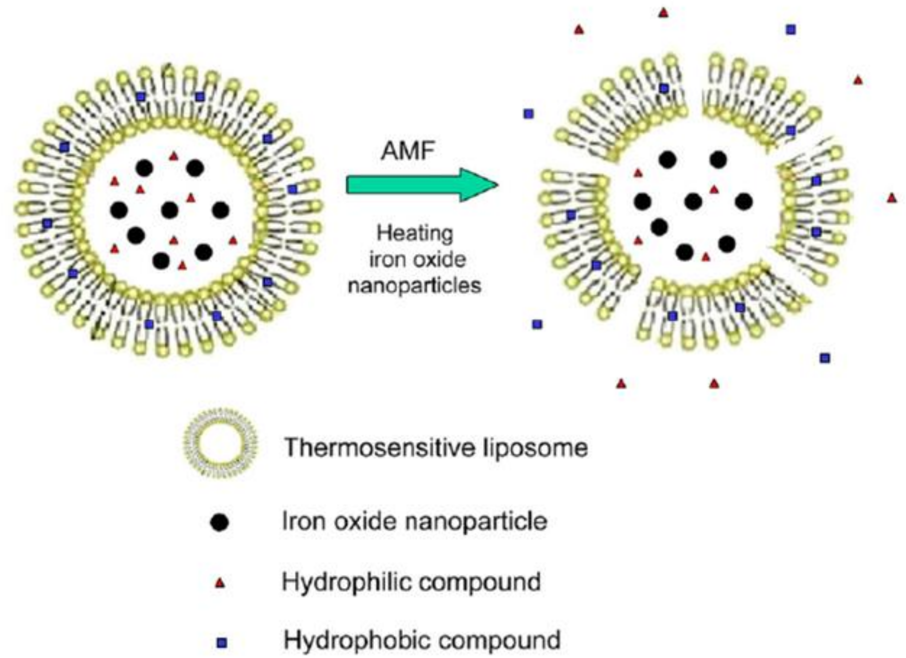
kinetic Monte Carlo

Magnetic fluid hyperthermia



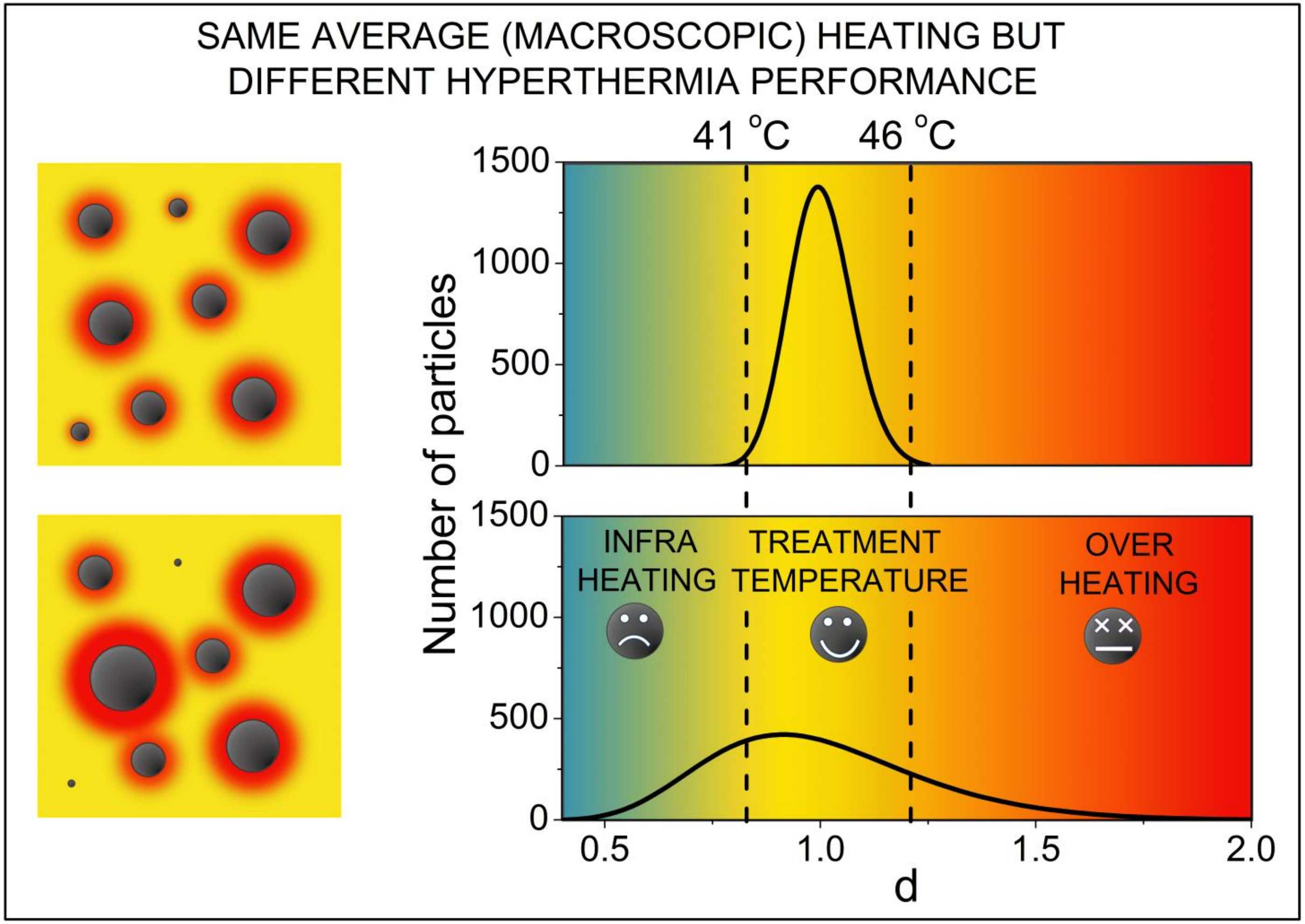
A. Andrade, et. al., Biomedical Enineering-
Frontiers and Challenges, 2011

Heat mediated drug delivery

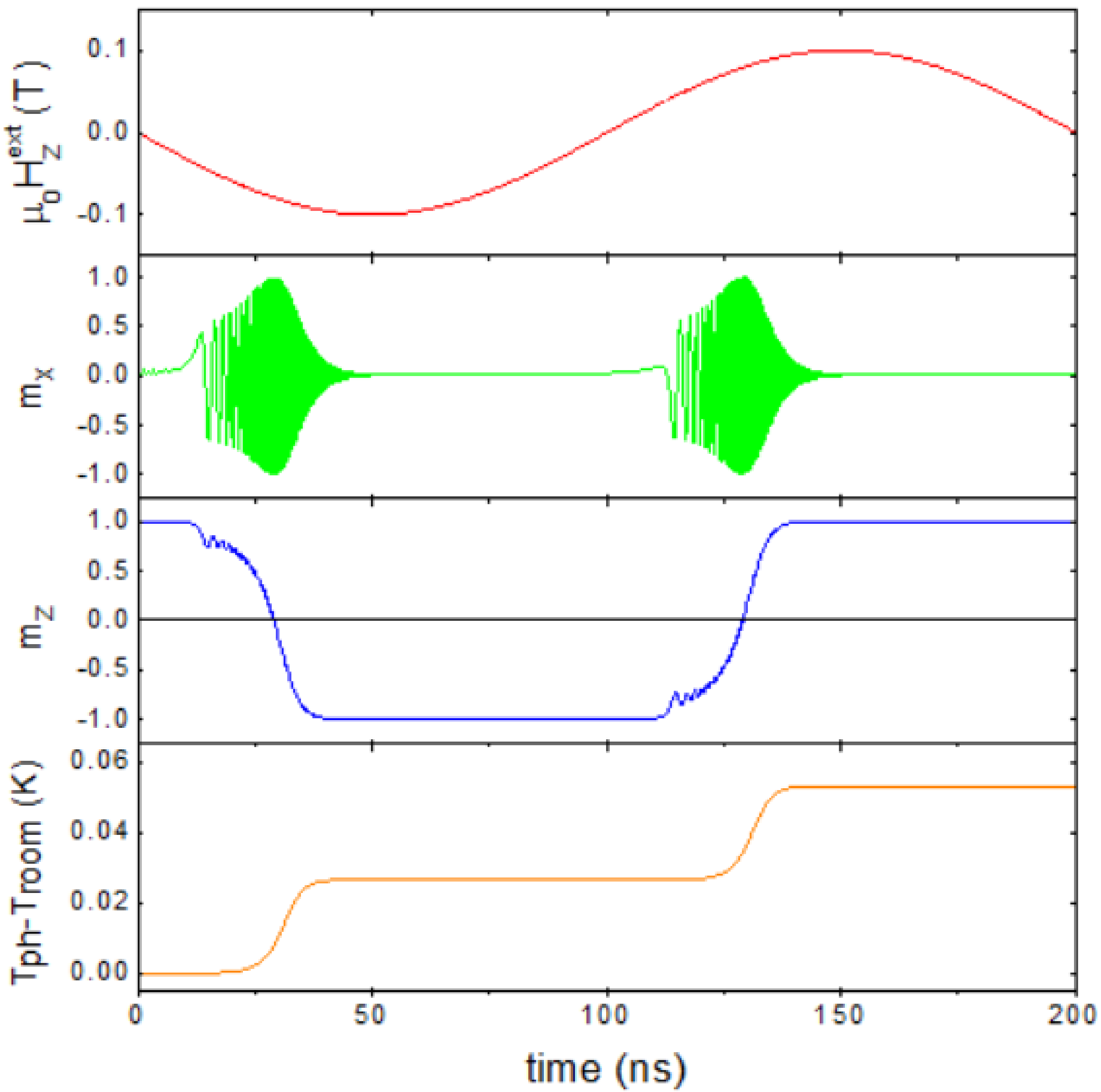


L.A. Tai, et. al., Nanotechnology, 2009, 20, 135101

Global *vs.* local heating

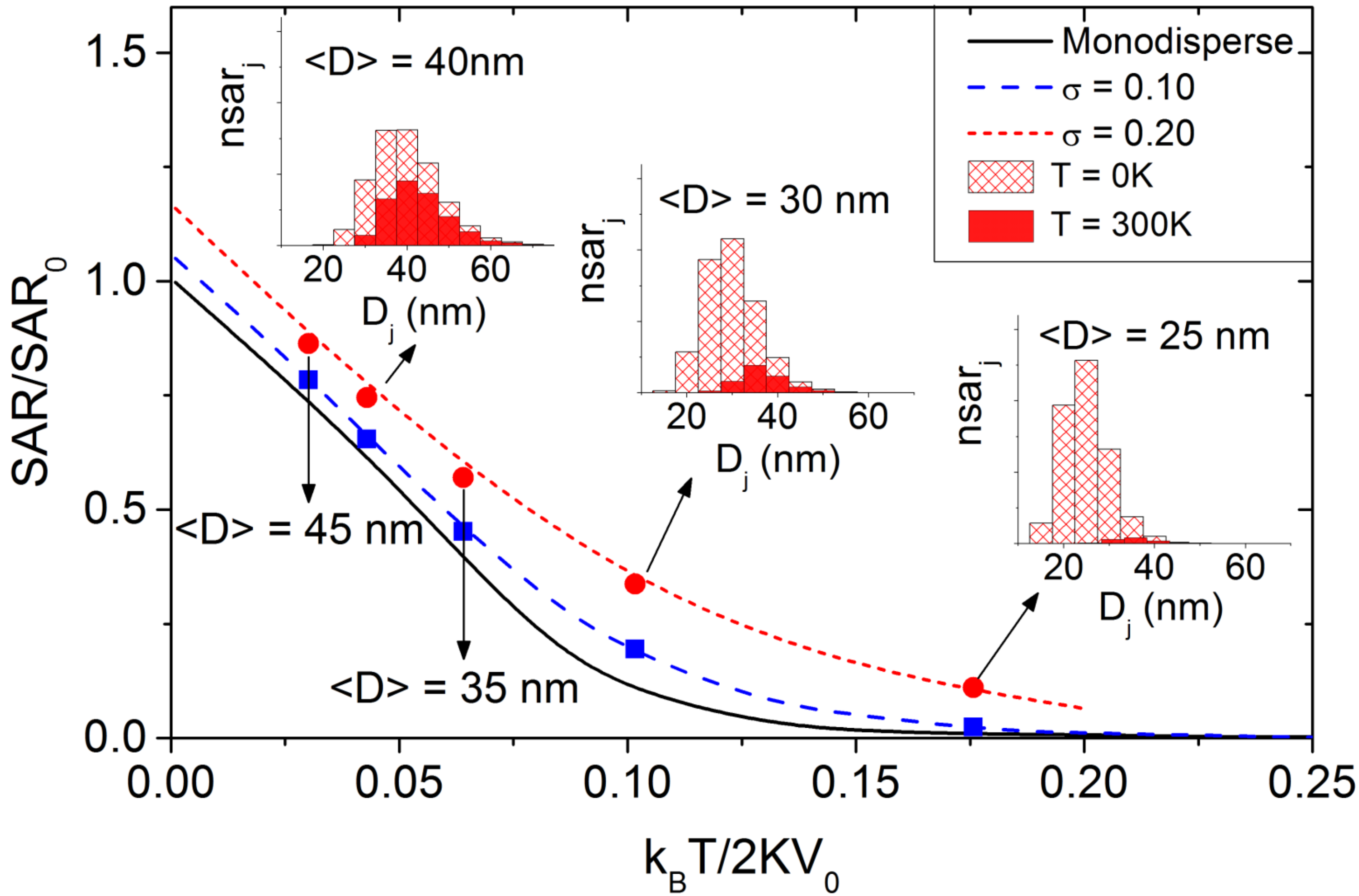


'The role of size polydispersity in magnetic fluid hyperthermia: average vs. local infra/over-heating effects', C. Munoz-Menendez, et. al., Phys. Chem. Chem. Phys., 2015, 17, 27812–27820



'Self-consistent description of spin-phonon dynamics in ferromagnets', P. Nieves, D. Serantes, O. Chubykalo-Fesenko, Phys. Rev. B, 2016, 94, 014409

Temperature effect → kMC for T>0K



'Distinguishing between heating power and hyperthermic cell-treatment efficacy in magnetic fluid hyperthermia', C. Munoz-Menendez, et. al., 2016, *Soft Matter,* 12, 8815-8818