

Physical potentials of radiofrequency hyperthermia with amplitude modulation

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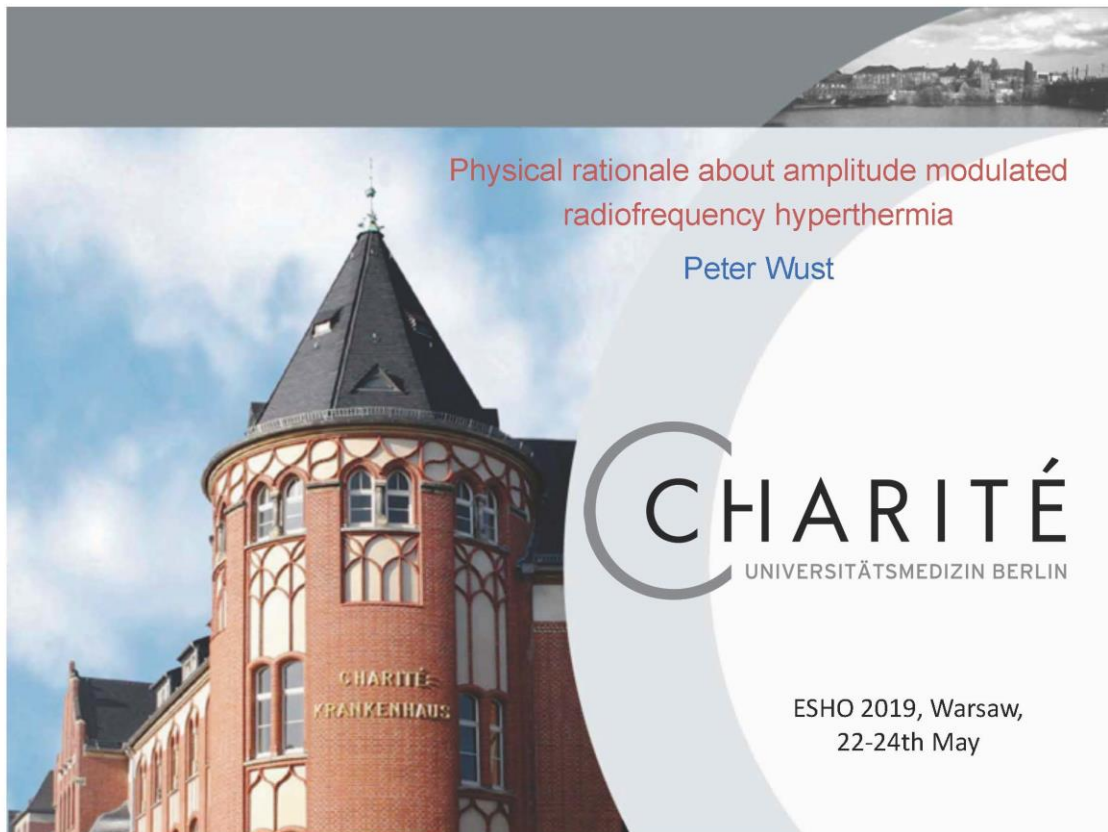
https://oncotherm.com/sites/oncotherm/files/2019-07/Physical_potentials_of_radiofrequency.pdf

Introduction: Preclinical studies and some clinical observations indicate that modulated electromagnetic hyperthermia (mEHT), which employs a radiofrequency (RF) carrier (13.56 MHz) with amplitude modulation (AM) at very low frequencies (VLF, <100kHz), enhances the effect of conventional mono-frequent RF hyperthermia. We conducted a physical evaluation to explore potential benefits of VLF modulation.

Methods: We reviewed the electrical behavior of cell suspensions, normal tissues and tumors at VLF (table). Then, we conceptualized microscopic models upon tumors and their microenvironment and analyzed the mechanism of power dissipation (conductive versus dielectric) specifically in tumors and normal tissues (muscle, organs, fat). We outline that cell suspensions as well as suitable tumors can ensure demodulation if the time constant RC of the equivalent circuit diagram of the tumor (resistivity R , capacitance C) and cycle duration $T_c=1/\Omega$ of the carrier at frequency Ω satisfy the relationship $RC \sim 2T_c$. R and C of different tissues (including tumor architectures) are estimated. Using this framework, we analytically solved the temperature/diffusion equation and calculated the magnitude of modulation-dependent thermal and non-thermal effects.

Results: We substantiate that additional VLF modulation can increase the specific absorption rate (SAR) in the extracellular fluid of tumors (necrosis formation) by a factor of 10 or even higher as compared to conventional mono-frequent RF hyperthermia. Such SAR-peaks can induce effective or even thermoablative temperatures (hot spots) in necrotic areas of millimeter to centimeter size typically disseminated over tumors. A relationship between SAR peak value [W/kg] and required minimum size of necrosis [mm] for relevant temperature increases (>43-44°C) can be derived (figure). In addition, we recognized that VLF modulation would have an electro-chemical effect at biological membranes in an extracellular medium caused by alternating ion currents. In particular, movements of the ions through the membrane can impair/destroy the disparate ion concentrations between vital cells and the surrounding extracellular fluid and can principally lead to cell death.

Conclusion: Our physical analysis suggests that RF hyperthermia with additional VLF-AM modulation is more effective against tumors than conventional RF hyperthermia due to thermal and non-thermal effects. Therefore mEHT should be further evaluated in prospective clinical trials.

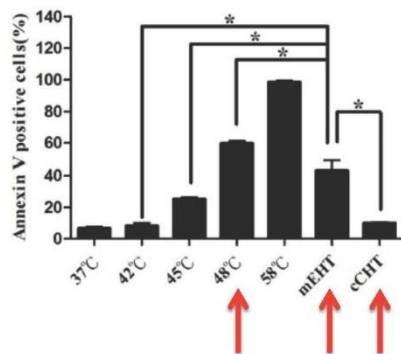


Present status of RF hyperthermia

Perfusion [ml/100g/min]	5	10	20
			Difficult-to-heat
SAR = 15 W/kg	42 °C	39.8 °C	38.6 °C
SAR = 30 W/kg	46.5 °C	42 °C	39.8 °C
SAR = 60 W/kg	55.5 °C	46.5 °C	42 °C
	Easy-to-heat		

Preclinical studies

In tumor cell suspensions differences of 6 °C were found comparing **waterbath/infrared** or **RF-heating** with **mEHT** at 13.56 MHz



Andocs et al 2009,

Yang et al 2016:

mEHT at 42 °C similar to
48 °C waterbath for cells,
superior to RF-CHT at 42°C

Clinical observations

Responses (PR, CR) after mEHT as mono-therapy
(brain tumors, liver metastases)

Fiorentini et al 2018:

Recurrent glioblastoma/astrocytoma after standard treatment

40 – 150 W mEHT mono-therapy (no chemotherapy),

CR 3/50, PR 14/50, SD 14/50, PD 17/50

Objective remissions in one third of the patients

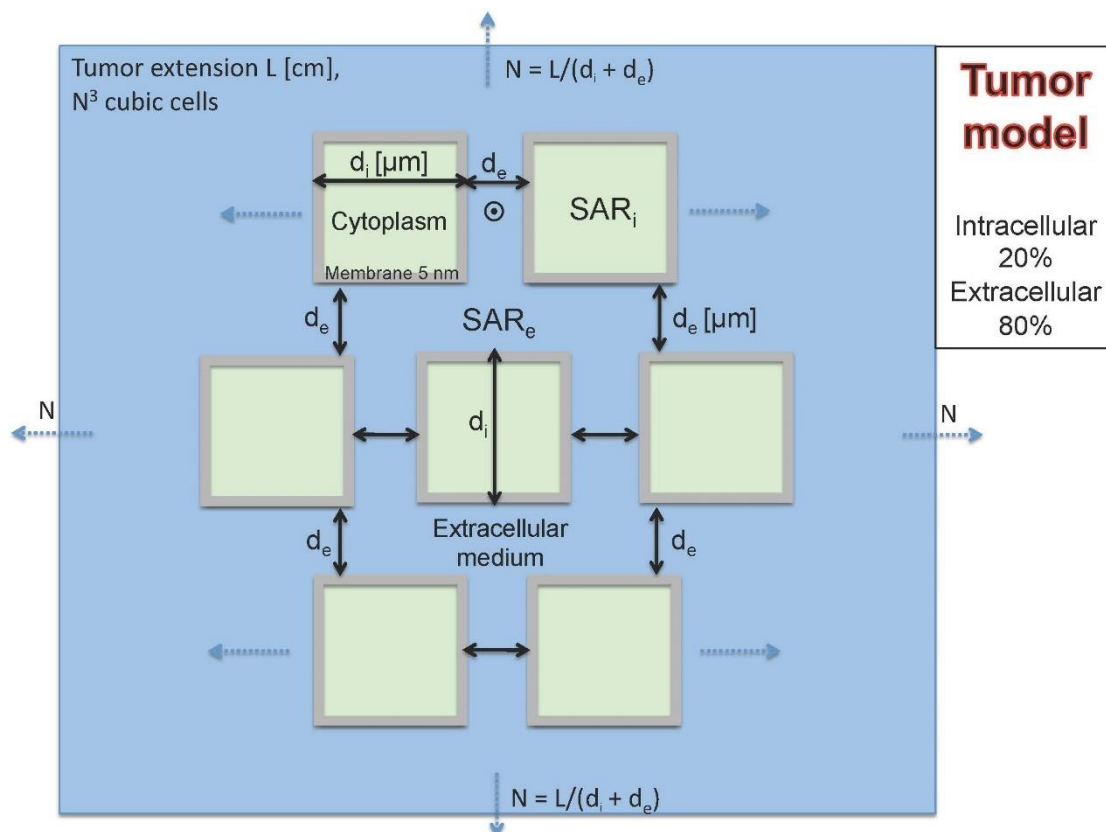
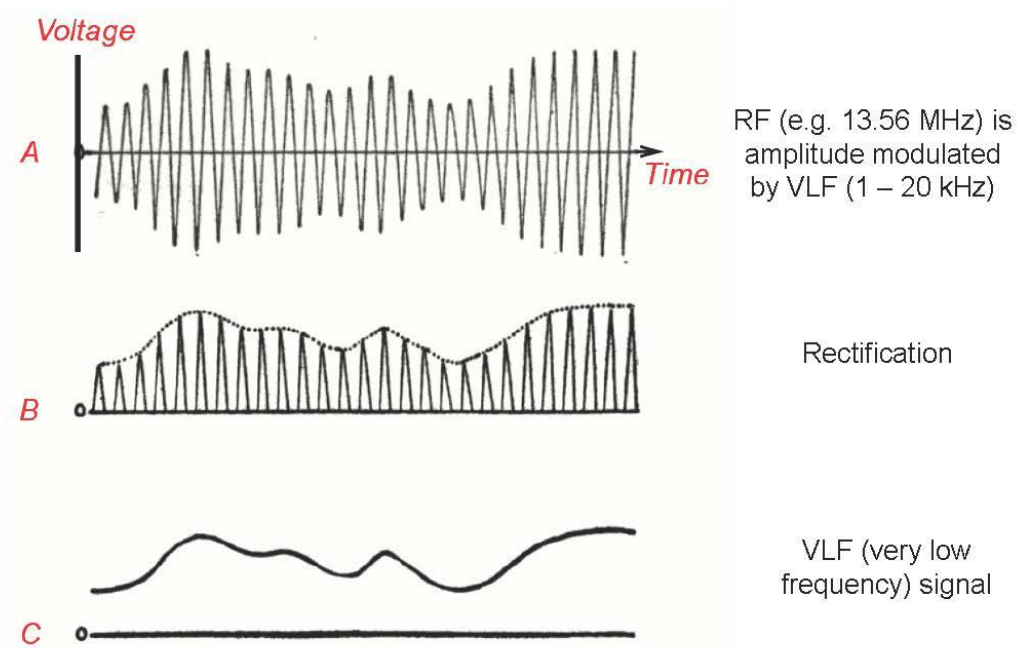
Minnaar et al 2019 (this congress):

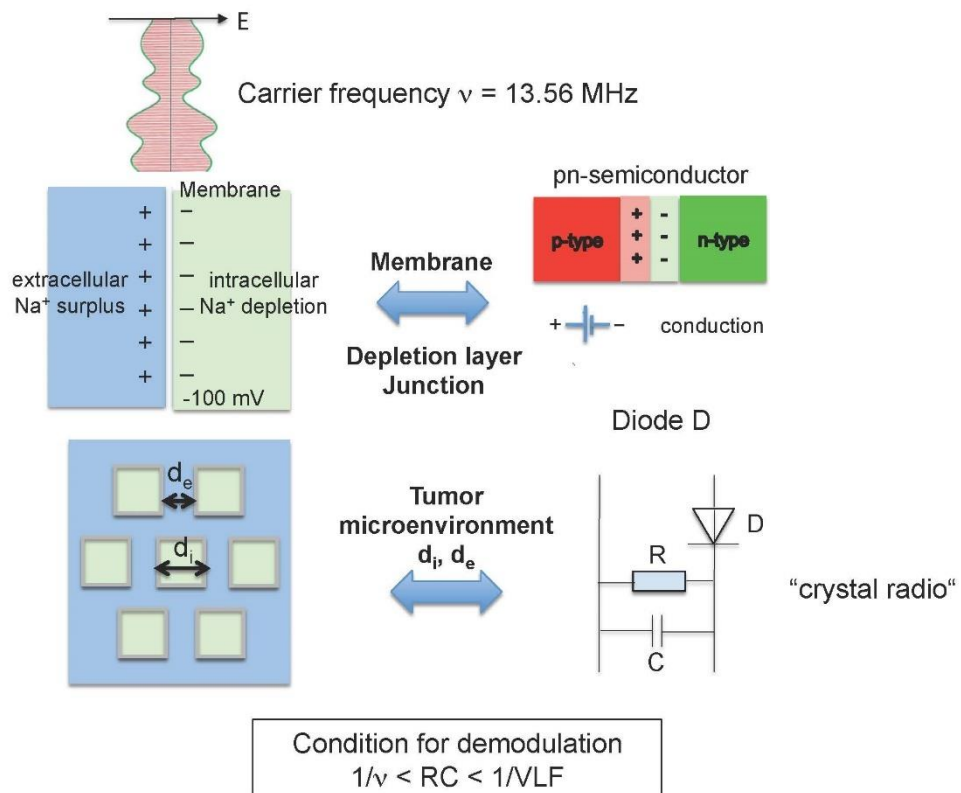
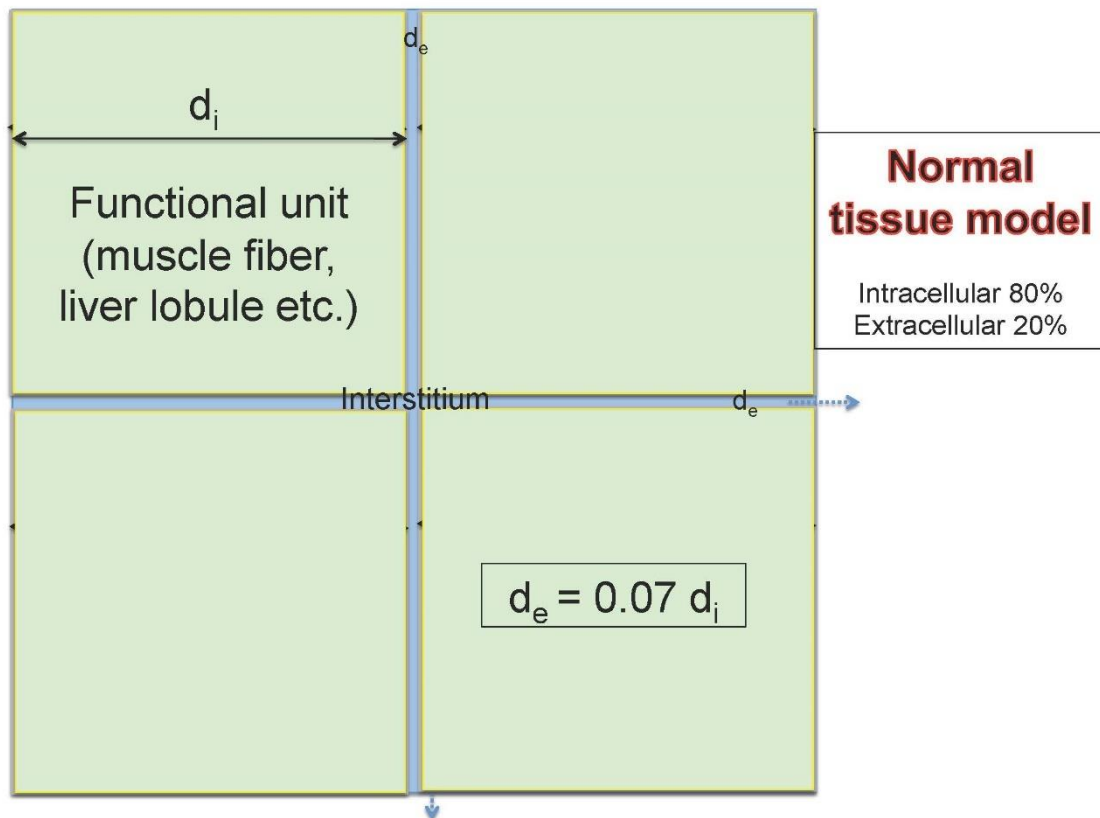
Phase III study upon cervical cancer using 130 W

RCT ± mEHT

Improved clinical endpoints

Is there a physical explanation for higher efficacy
in tumors, if we use AM-modulated RF?





$\kappa = 0.6 \text{ W/m}^\circ\text{C}$	Thermal conductivity (tumor)	Data from Kotnik, Miklavcic 2000
$\rho = 1.0 \text{ kg/l}$	Density (water)	
$c = 4,000 \text{ Ws/kg}^\circ\text{C}$	Heat capacitance (tumor)	
$\sigma_e = 1.2 \text{ S/m}$	Extracellular medium conductivity (DC – 100 MHz)	
$\sigma_i = 0.3 \text{ S/m}$	Cytoplasm conductivity (DC – 100 MHz)	
$\sigma_m = 3 \times 10^{-7} \text{ S/m}$	Membrane conductivity (< 1 MHz)	
$c_m = \epsilon_m/d = 0.9 \times 10^{-2} \text{ F/m}^2$ $\approx 1 \text{ } \mu\text{F/cm}^2$	Membrane capacitance $\epsilon_m = 4.4 \times 10^{-11} \text{ As/Vm}$, $d = 5 \text{ nm}$ (membrane)	
$\epsilon_{r/e} = 72.5$	Extracellular medium relative permittivity (DC – 100 MHz)	
$\epsilon_{r/i} = 72.5$	Cytoplasm relative permittivity (DC – 100 MHz)	
$\epsilon_{r/m} = 5$	Membrane relative permittivity (< 10 MHz)	
$\mu = 4.6 \times 10^{-8} \text{ m}^2\text{V}^{-1}\text{s}^{-1}$ $\mu = 6.75 \times 10^{-8} \text{ m}^2\text{V}^{-1}\text{s}^{-1}$ $\mu = 6.85 \times 10^{-8} \text{ m}^2\text{V}^{-1}\text{s}^{-1}$	Mobility of Na^+ ions in water Mobility of K^+ ions in water Mobility of Cl^- ions in water	Foster, Schwan 1989
$E = 100 - 300 \text{ V/m}$	E-field for SAR = 10 – 60 W/kg $E = 200 \text{ V/m}$ for SAR = 25 W/kg	
$v = \mu \times E$	Drift velocity [m/s]	
$\tau = d^2 \rho c / \kappa$	Relaxation time for hot spot of extension d $\tau = 10 \text{ s}$ for $d = 1 \text{ mm}$ $\tau = 10^{-1} \text{ s}$ for $d = 100 \text{ } \mu\text{m}$ $\tau = 10^{-3} \text{ s}$ for $d = 10 \text{ } \mu\text{m}$ $\tau = 10^{-9} \text{ s}$ for $d = 10 \text{ nm}$	

Capacitance in the tumor (d_e , d_i [μm])

$$C_{Tm} = N \times C_{cell} = L[\text{cm}] \times d_i^2 / (d_i + d_e) \times 0.05 \text{ nF}$$

Resistance in the tumor (d_e , d_i [μm])

$$R_{Tm} = (L/F) \times \sigma = (1/L[\text{cm}]) \times 100 \text{ ohm}$$

Time constant (with d [μm])

$$RC = d_i^2 / (d_i + d_e) \times 0.05 \times 10^{-7} \text{ s}$$

Note:

RC is independent of tumor size L and is therefore a **local parameter** characterizing the *microenvironment* and *electrical behavior* in this part of the tumor.

Thus in every part of the tumor *demodulation* occurs, if the condition is met

$$1/f_{\text{carrier}} < RC < 1/f_{\text{mod}}$$

Inspecting the condition for demodulation in an *envelope detector* (crystal radio, detector receiver)

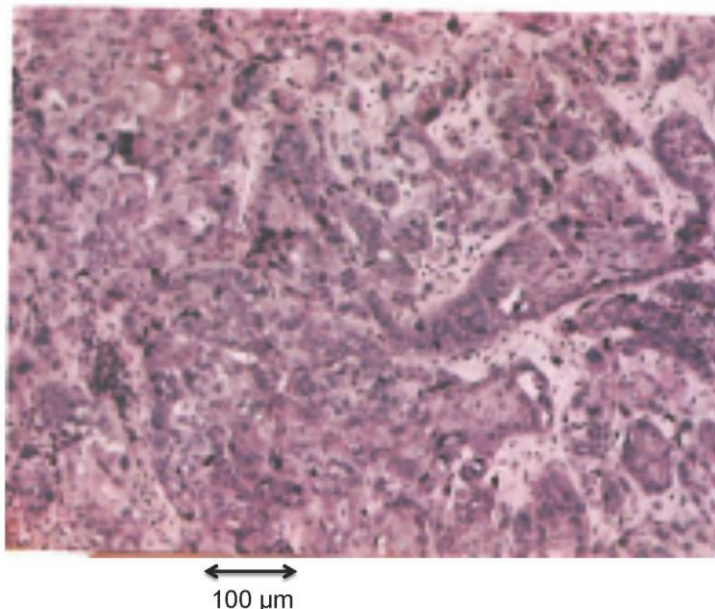
$$1/f_{\text{carrier}} < RC < 1/f_{\text{mod}}$$

$$\text{E.g. } f_{\text{carrier}} = 10 \text{ MHz, } f_{\text{mod}} = 10 \text{ kHz} \\ 10^{-7} \text{ s} < RC < 10^{-4} \text{ s}$$

According to the inequation larger f_{carrier} might be even better.

It is seen that for small d_i (10 – 20 μm) and large d_e RF towards 100 MHz is a suitable carrier frequency.

A squamous cell carcinoma is composed of cell clusters of 10 - 100 μm size or larger with chaotic structure



The extracellular space is a conducting medium and the current path is narrowed, which locally increases the SAR

Characteristics of AM-RF

Demodulation preferentially occurs in the microenvironment of tumors (and much less in normal tissues)

SAR(VLF) at *audio frequencies* (1 – 20 kHz) is deposited at the membranes (where rectification and demodulation occurs)

SAR(VLF) might be concentrated in a small volume at the membrane

Membranes are *isolators* in the VLF-range (negligible intracellular power dissipation)

Conductive power dissipation is dominant in the extracellular medium with high $\sigma = 1.2 \text{ S/m}$.

Non-temperature dependent effects in the VLF-range should be considered.

Electrochemical effect at VLF caused by a drift of the ions Na^+ and Cl^- in the extracellular electrolyte solution exposed to E (with mobility μ)

$$\text{deflection } \delta[\mu\text{m}] = E[\text{V/m}]/40 \times \text{VLF}[\text{Hz}]$$

Na^+ ions are crossing the membrane for $\delta > \text{some nm}$

Modulation frequency	Deflection for E = 200 V/m SAR = 25 W/kg	Deflection for E = 1,200 V/m SAR = 1,000 W/kg
1 Hz	5 μm (part of cell)	30 μm (cell)
10 Hz	500 nm (part of cell)	3 μm (part of cell)
100 Hz	50 nm (>> membrane)	300 nm (part of cell)
1 kHz	5 nm (membrane)	30 nm (>> membrane)
10 kHz	0.5 nm (< membrane)	3 nm (membrane)
100 kHz	0.05 nm (<< membrane)	0.3 nm (< membrane)

Conclusions:

AM-RF is an interesting approach to increase efficacy in tumors employing their typical microenvironment

It seems promising to explore the suitable frequencies for *modulation* (some kHz?) and for the *carrier* (10 – 100 MHz?)

Our physical analysis supports the view that non-temperature dependent effects might be relevant (especially electrochemical effects)

Biology is with us, but physics is against us

What if the saying were:

Physics is our friend, but we have not noticed it.

It would be unrequited love (and tragic).