Looking Deeper into UV-MALDI with Numerical Models

(and experiments)

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NIST MALDI Workshop 2005

What do we want from MALDI?

Sensitivity

Generality or Specificity

Reproducibility

Quantitation

HOW DOES IT WORK?

Modelling UV-MALDI

Matrix ionization mechanisms

Consequences of the phase change

Analyte ionization mechanisms

Quantitative predictions

The 2-Step Continuum Model

Laser pulse: nanoseconds

Expansion to collision-free: microsec.

1) Primary ionization: during or shortly after the laser pulse.

2) Secondary ionization: ion-molecule reactions in the expanding plume.

Possible UV Primary Mechanisms

Exciton pooling: 2-center

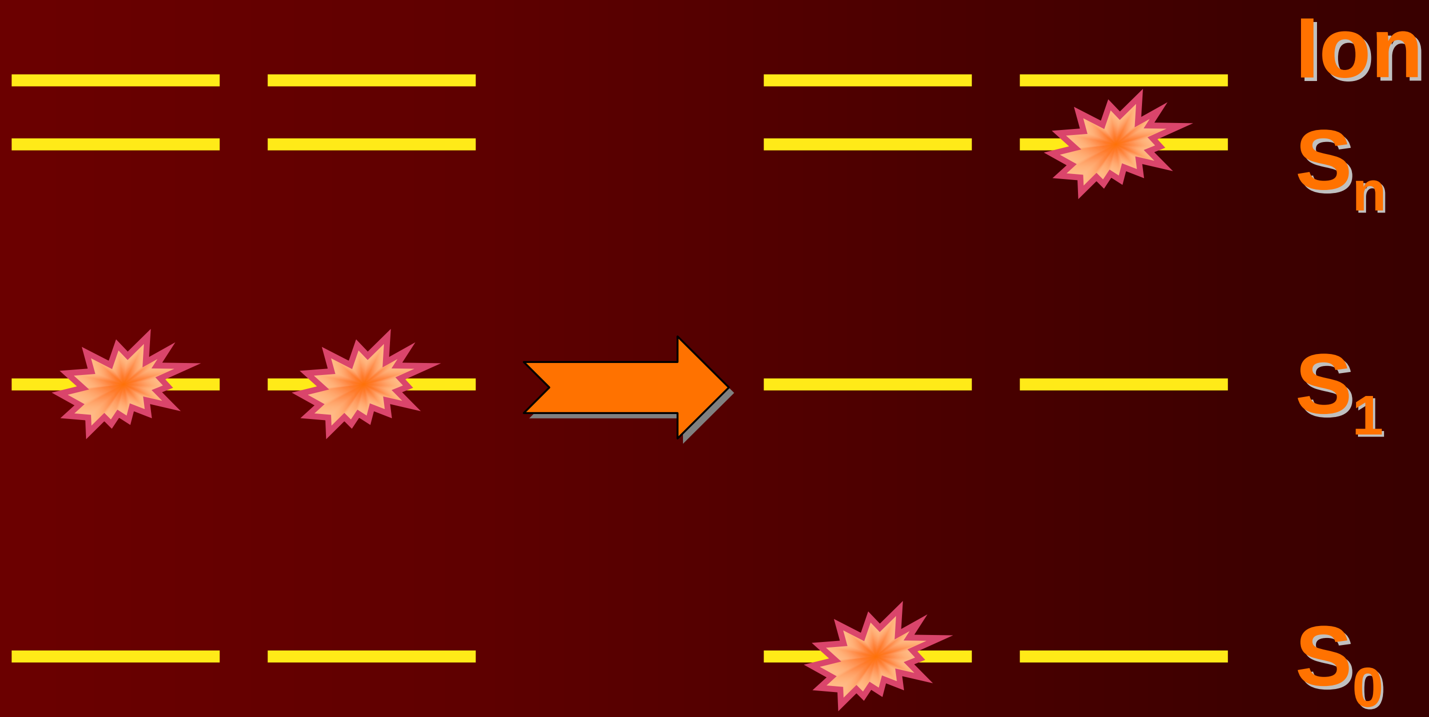
Two-photon ionization: 1-center

Excited state proton transfer

Preformed ions

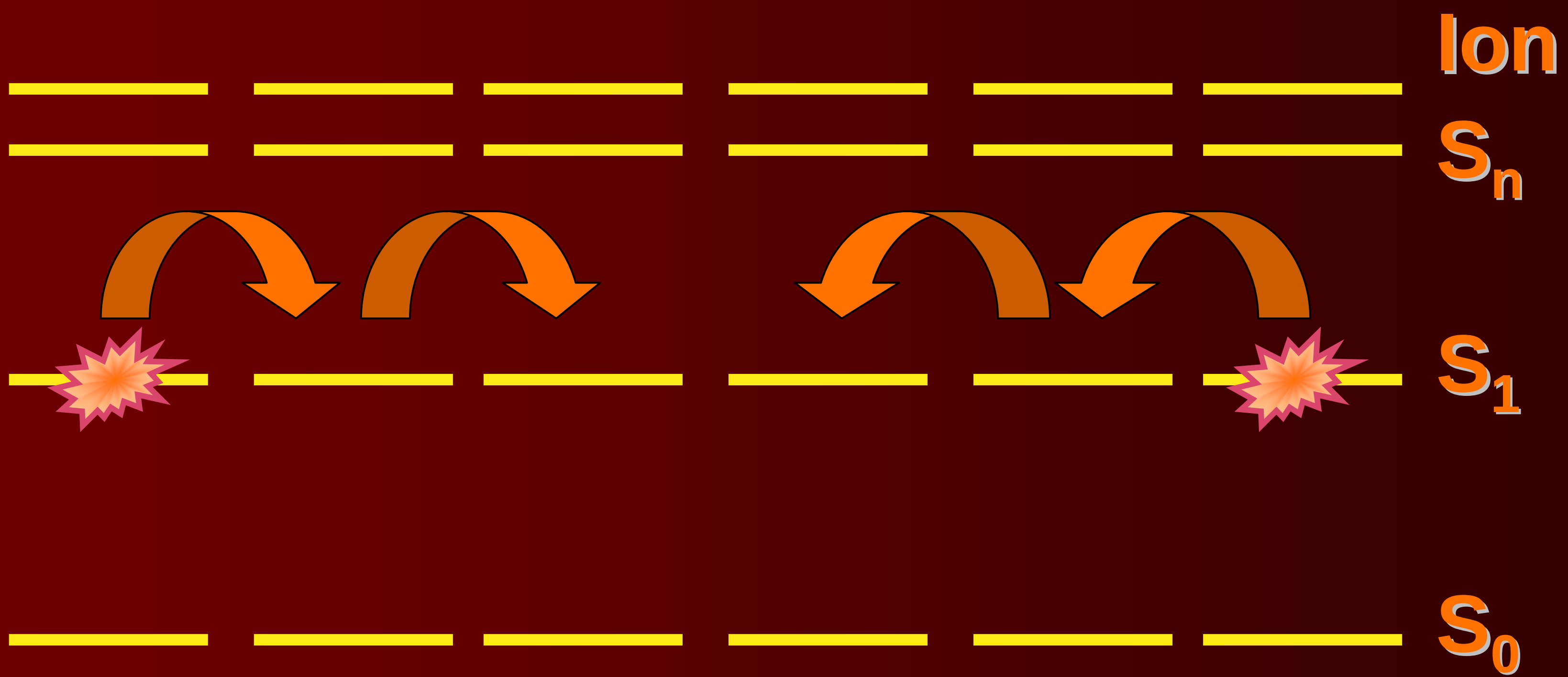
. . . .

S_1+S_1 Exciton Pooling



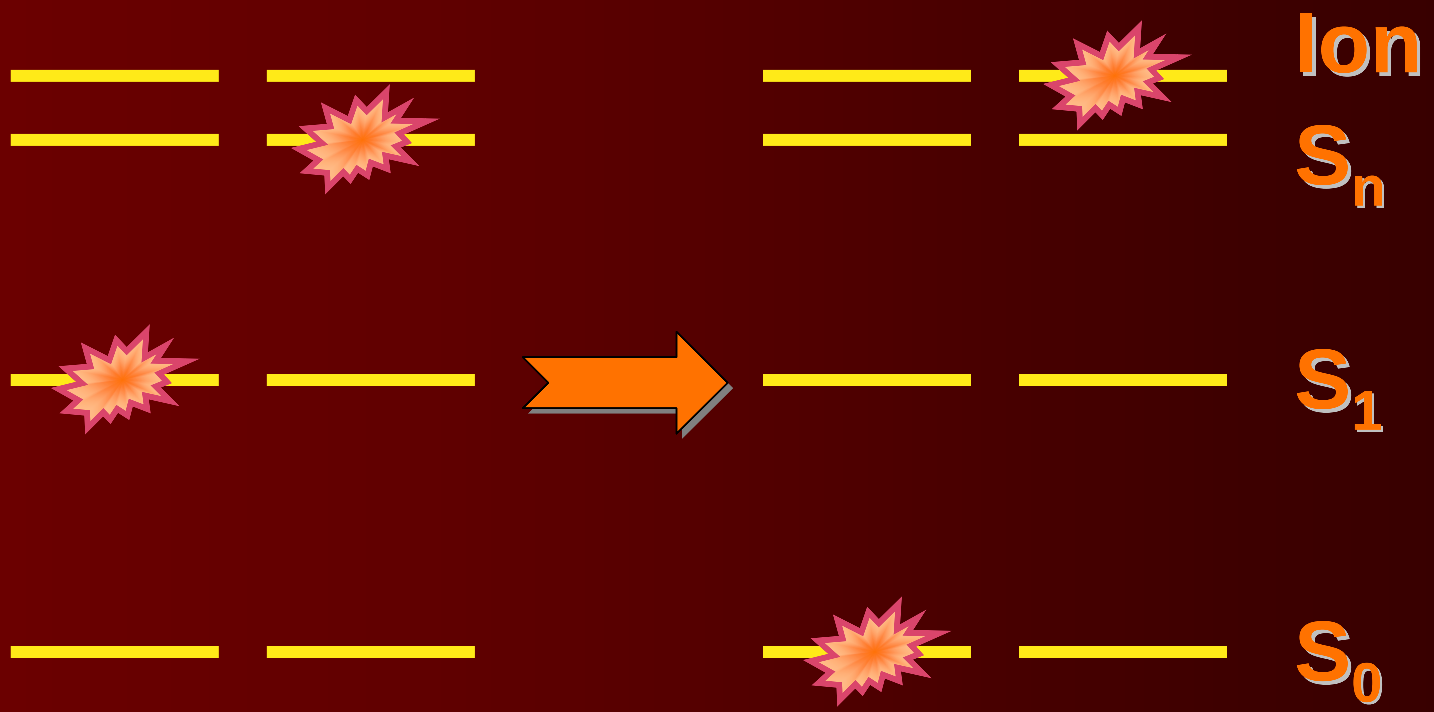
2 neighboring matrix molecules

Exciton Diffusion & Pooling

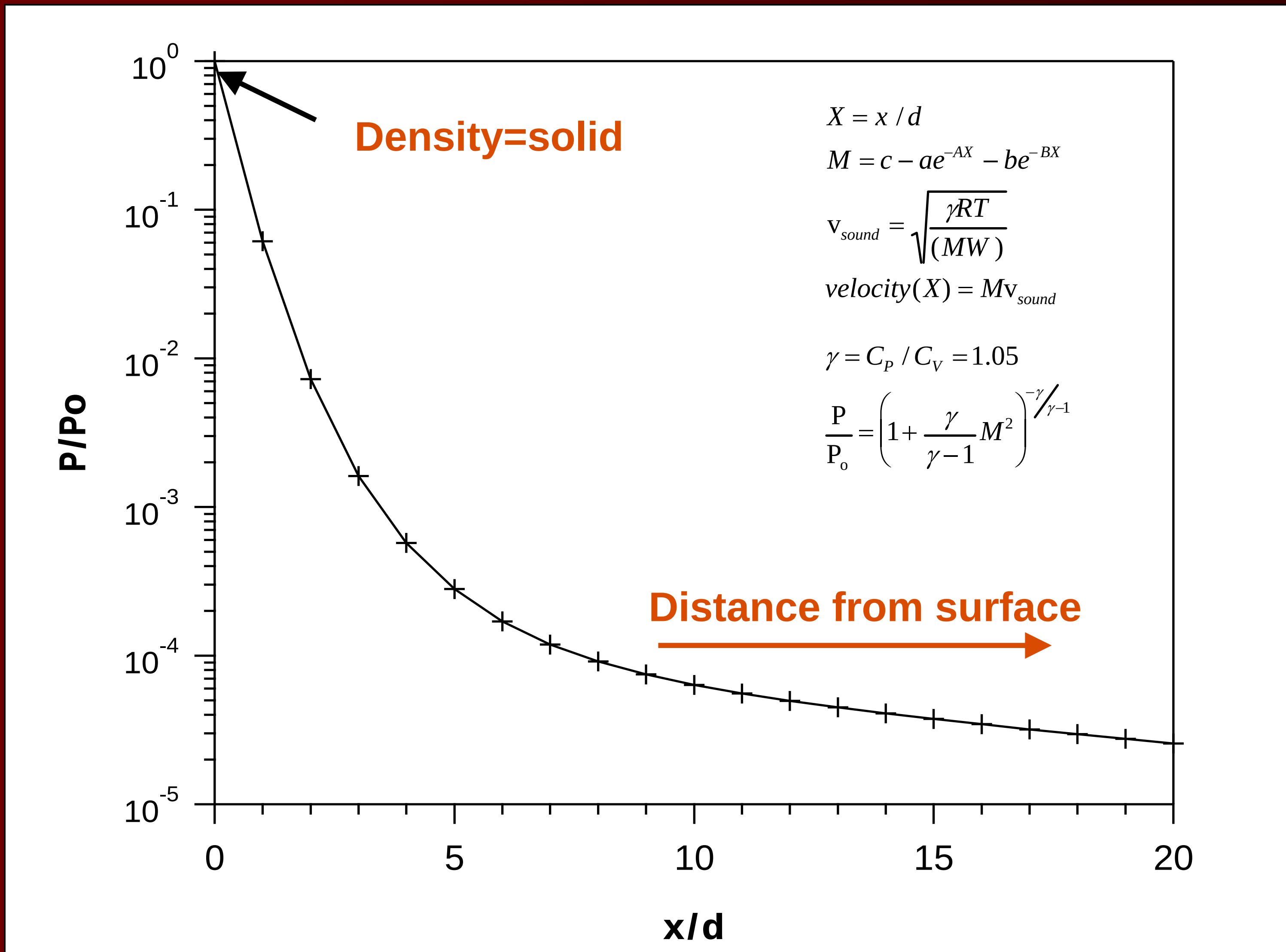


2 DISTANT matrix molecules

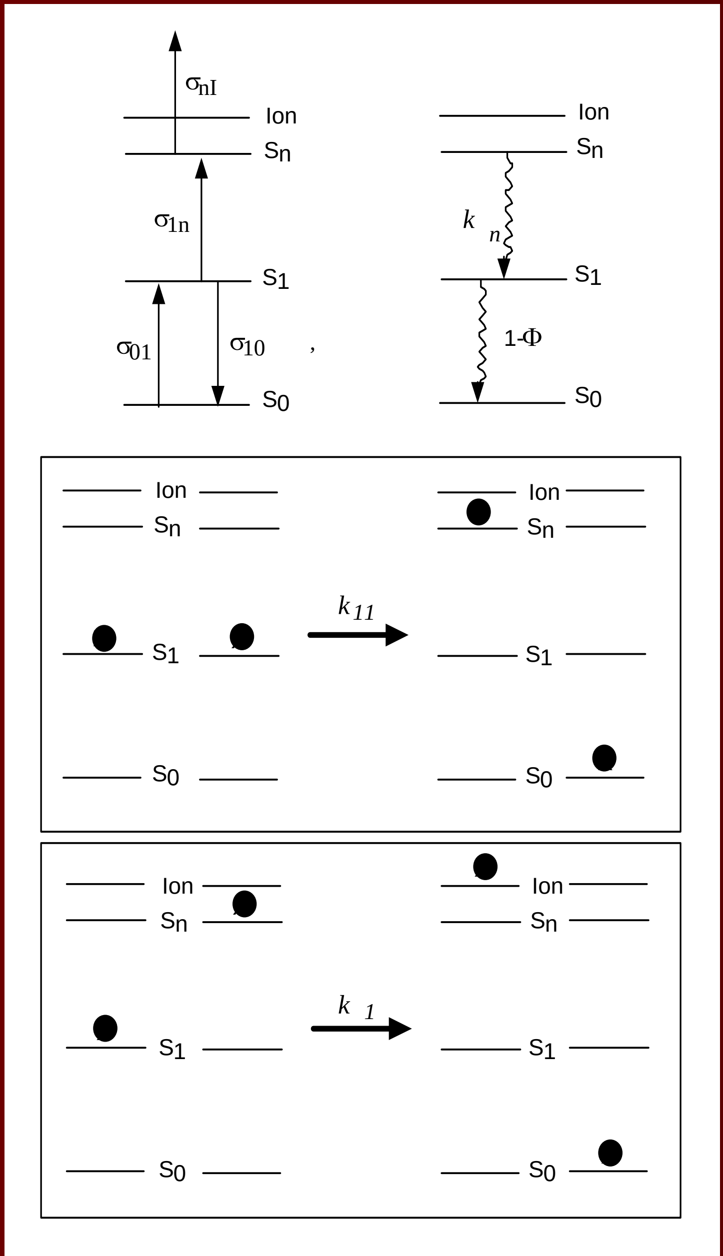
S_1+S_n Exciton Pooling



Adiabatic Plume Expansion



Continuum Model Matrix Processes



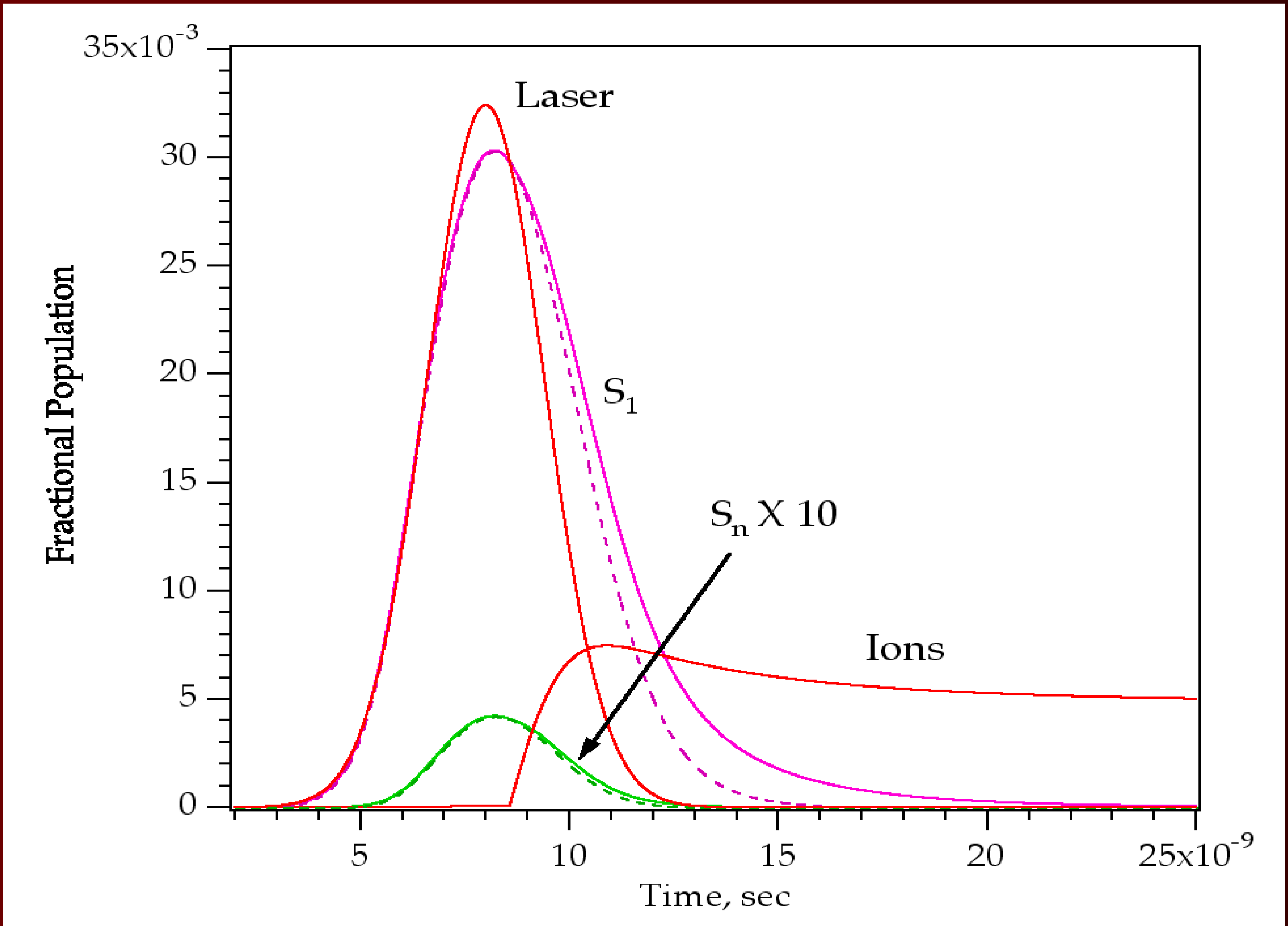
Parameters for DHB MALDI at 355 nm.

IP (free molecule)	8.05 eV
IP (large clusters)	7.82 eV
S_1 state energy	3.466 eV
starting temperature	298 K
σ_{01}= S_0–>S_1 absorption coeff.	9.9 X10^{-18} cm^2
σ_{10}= S_0<-S_1 stimulated emission	2 X10^{-18} cm^2
σ_{1n}= S_1–>S_n absorption coeff.	2 X10^{-18} cm^2
k_{n1}= S_1–>S_n decay rate	7.5 X10^{10} s-1
τ_1(t=0)= solid state S1 lifetime	1 ns
τ_1'= limiting plume S1 lifetime	3 ns
Φ(t)= fluorescence quantum yield	$\tau_1(t)/\tau_1'$
f= internal degrees of freedom	45 (normal modes)
γ= C_p/C_v for plume expansion	1.05 (from d.f.)
density	1.44 g/cm^3
k_{I0} = Ion recombination	1.5 X10^{11} s^{-1}
Fraction clusters in plume	0.85
laser spot diameter	0.1 mm

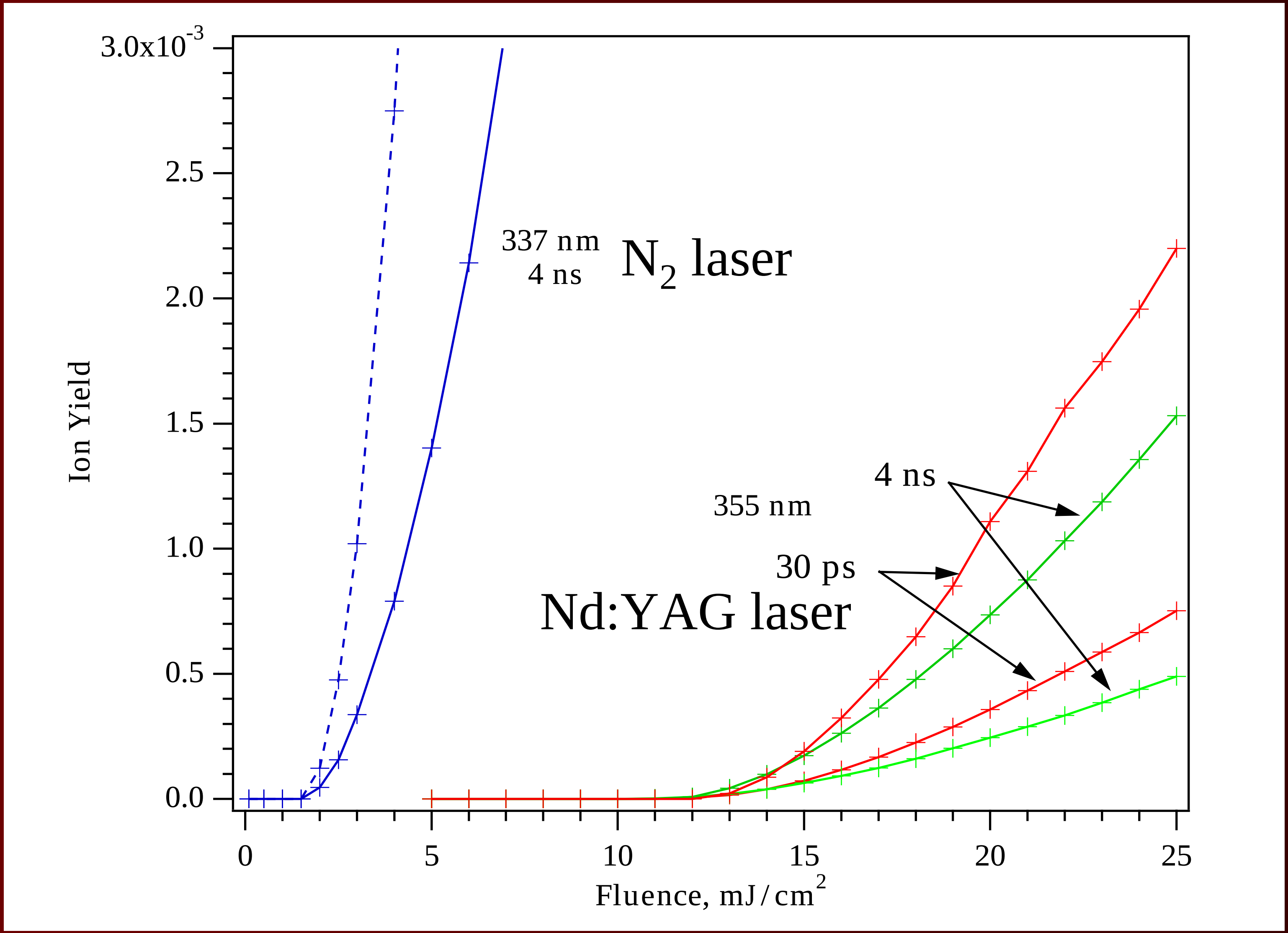
Pooling rate constants:

k_{l1} = S_1 + S_1–>Sn + S_0	7 X10^9 s^{-1}
k_{In} = S_1 + S_n–>Ions + S_0	1 X 10^{11} s^{-1}
D= expansion scaling factor	P/P_0

Example Results



Wavelength, Fluence, and Pulse Length Effects



Model Results Matrix Only

1) Magnitude of the ion yield: order 10^{-2}-10^{-4}
2) Plume temperatures: 500-600 K
3) Velocity distribution: 500-1200 m/s
4) Fluence, rather than irradiance threshold
5) Existence of a fluence threshold
6) Position of the threshold
7) Spot size effect on apparent threshold
8) Wavelength dependence of threshold + yield
9) Existence of 2-pulse effect
10) Time of the 2-pulse maximum
11) Fluorescence quenching vs. Fluence
12) Electron & ion yields: thick vs. thin sample
13) Sample temperature effects
14) Metal substrate effects ....

WIDE-RANGING QUANTITATIVE AGREEMENT WITH DATA

Matrix-Analyte Secondary Reactions

Mechanisms:

- Proton transfer
- Electron transfer
- Cationization

In a sufficiently dense plume these can be treated by gas-phase thermodynamics

Adding Analyte to the Continuum Model

$M^+ + A \Leftrightarrow M + A^+$

$$\frac{d[\mathrm{A}]}{dt} = -k_{MA}\left[\mathrm{M}^+\right][\mathrm{A}] + k_{AM}[M]\left[\mathrm{A}^+\right]$$

$$\frac{d\left[\mathrm{A}^+\right]}{dt} = k_{MA}\left[\mathrm{M}^+\right][\mathrm{A}] - k_{AM}[M]\left[\mathrm{A}^+\right]$$

Arrhenius Rates:

$$k_{MA} = Ae^{-EA/kT} \qquad k_{AM} = Ae^{-(EA+\Delta G)/kT}$$

$$A = \pi(D_M + D_A)^2 F(1-F)n\sqrt{V_M{}^2 + V_A{}^2}$$

Activation Energy:

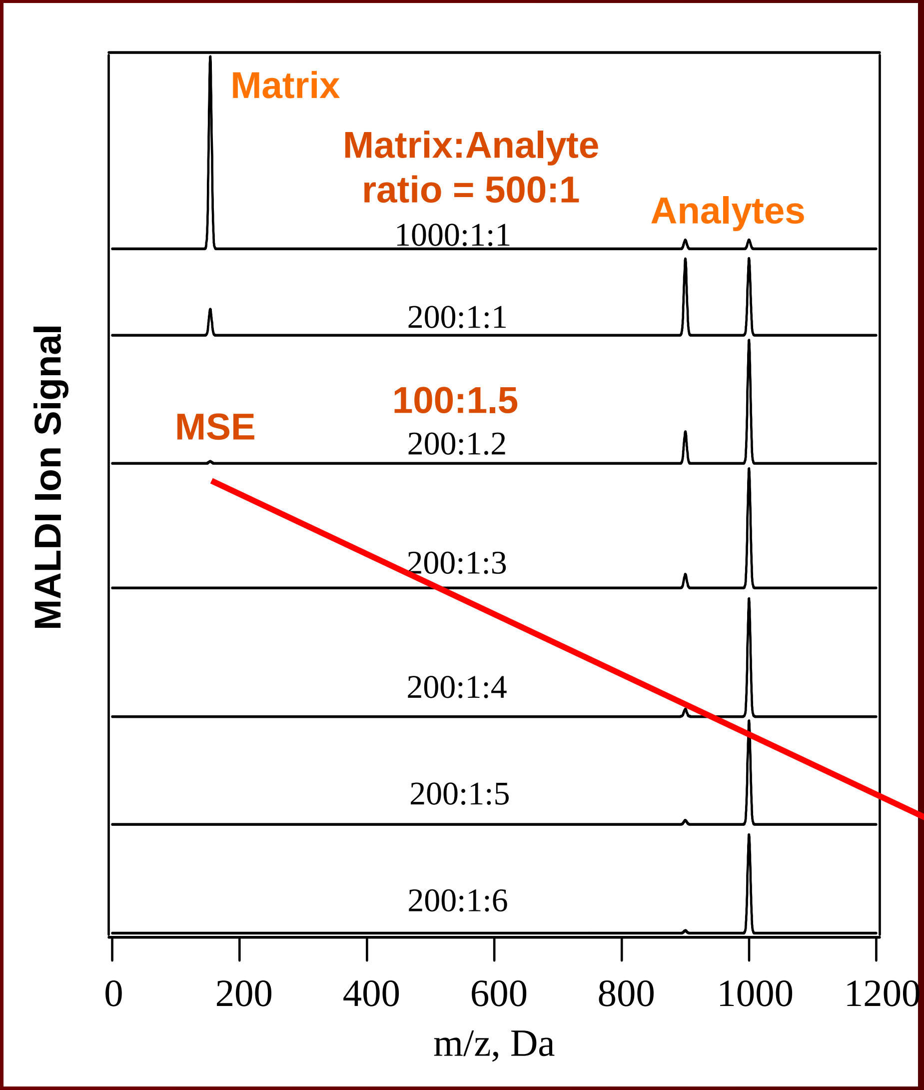
$$EA = \Delta G - \lambda \ln\left(\frac{1}{1+e^{-\Delta G/\lambda}}\right)$$

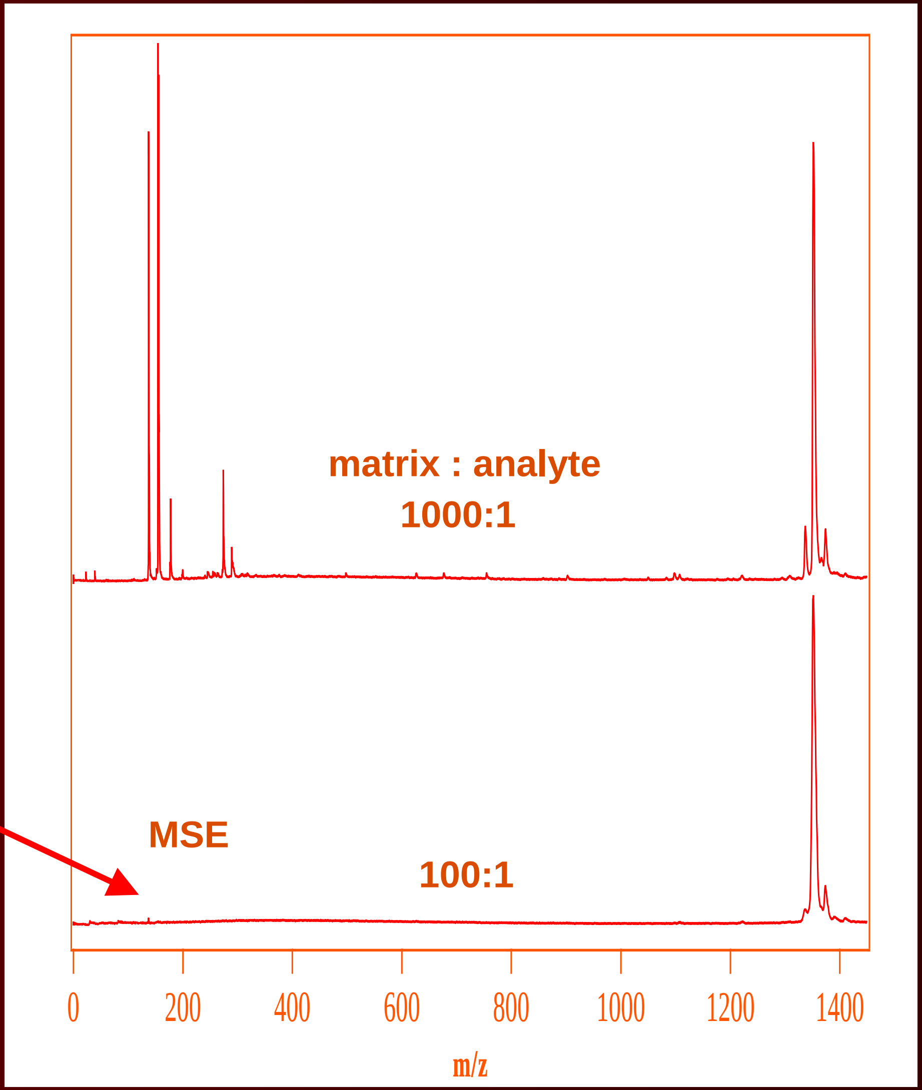
Volume Correction:

$$\left\lfloor 1 + \left[\left(\frac{D_A}{D_M}\right)^2 - 1\right]\frac{P}{P_0}\right\rfloor$$

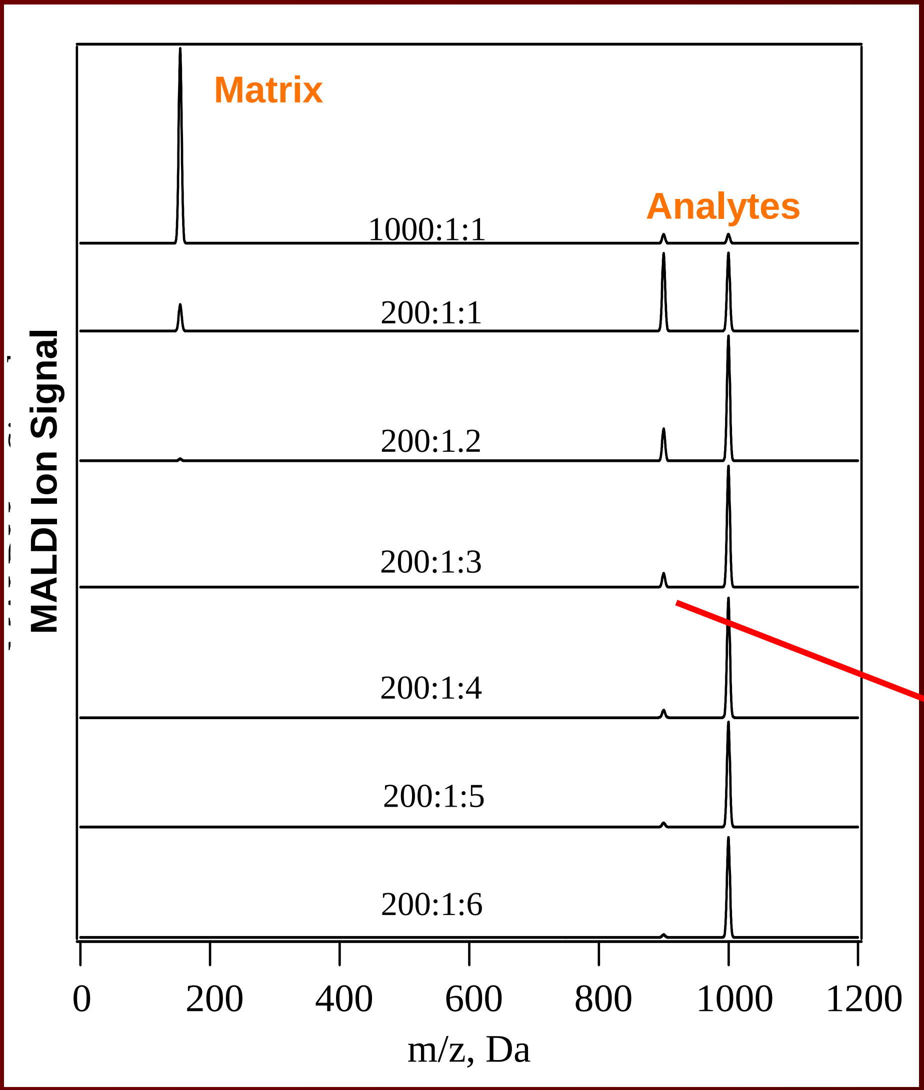
No adjustable parameters

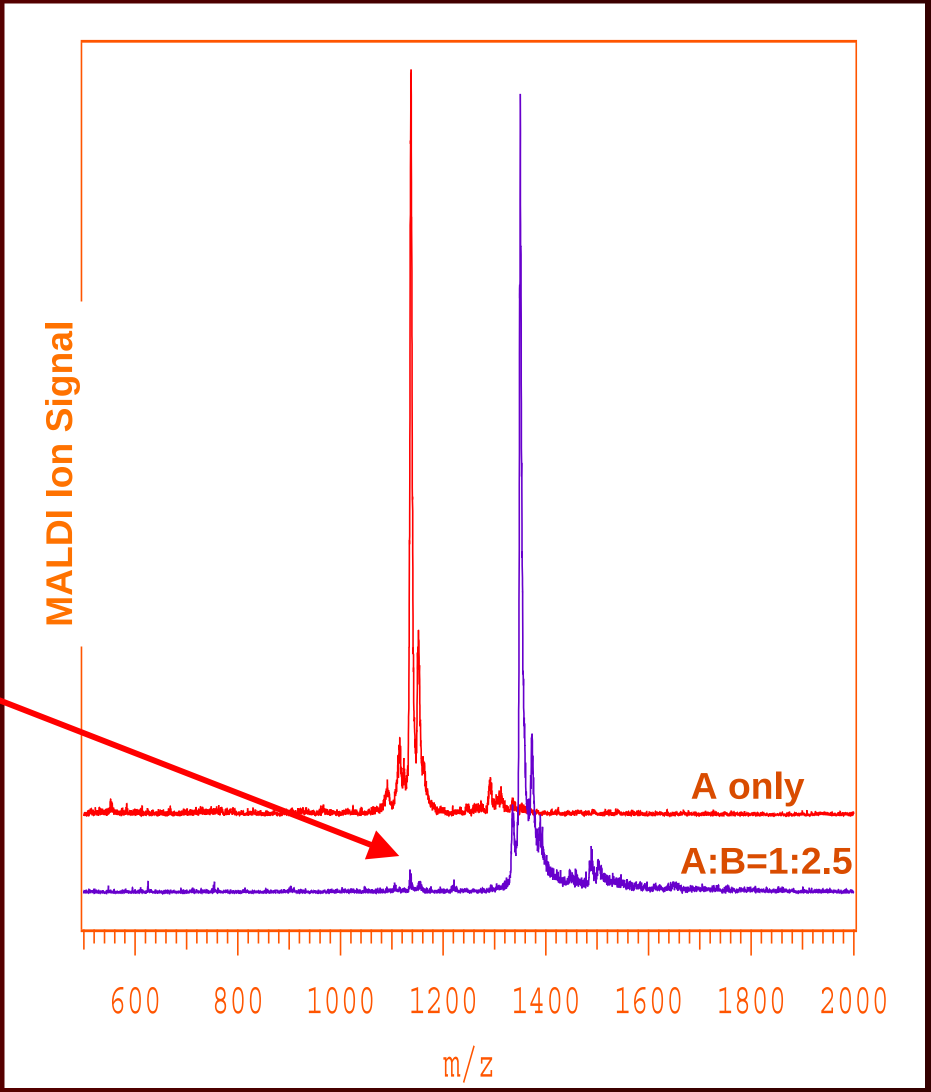
Matrix Suppression Effect





Analyte Suppression Effect

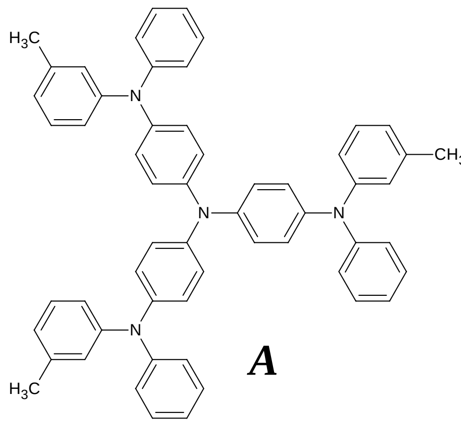




Model Results, Matrix & Analyte

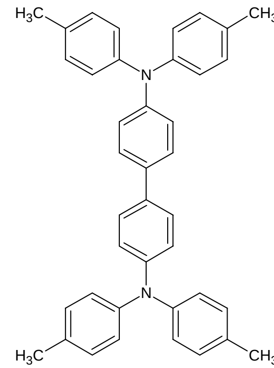
- Existence of MSE + ASE
- Characteristics of MSE + ASE vs.:
    - Molecular weight
    - Fluence
    - Concentration- absolute & relative
    - ΔG of charge transfer reaction
- Valid for
    - cationization
    - (de)protonation
    - electron transfer
- Quantification of ion suppression effects
- ...
- Wide-ranging quantitative agreement with data.
- Predictive capability.
- Rational matrix choice for desired analyte.

Electron Transfer MALDI



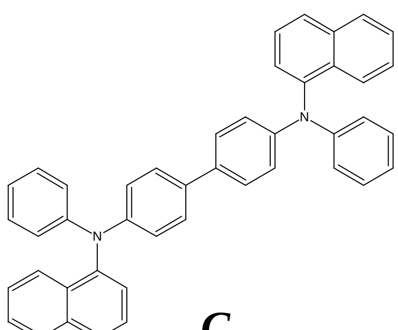
A

CAS#: 124729-98-2



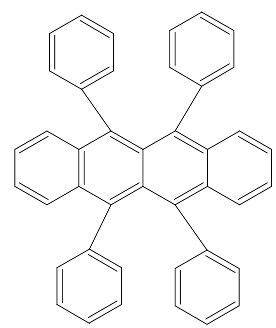
B

CAS#: 76185-65-4



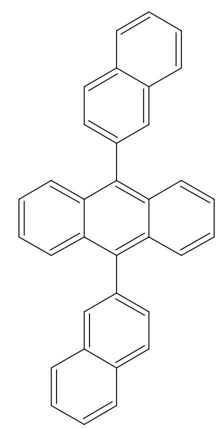
C

CAS#: 123847-85-8



D

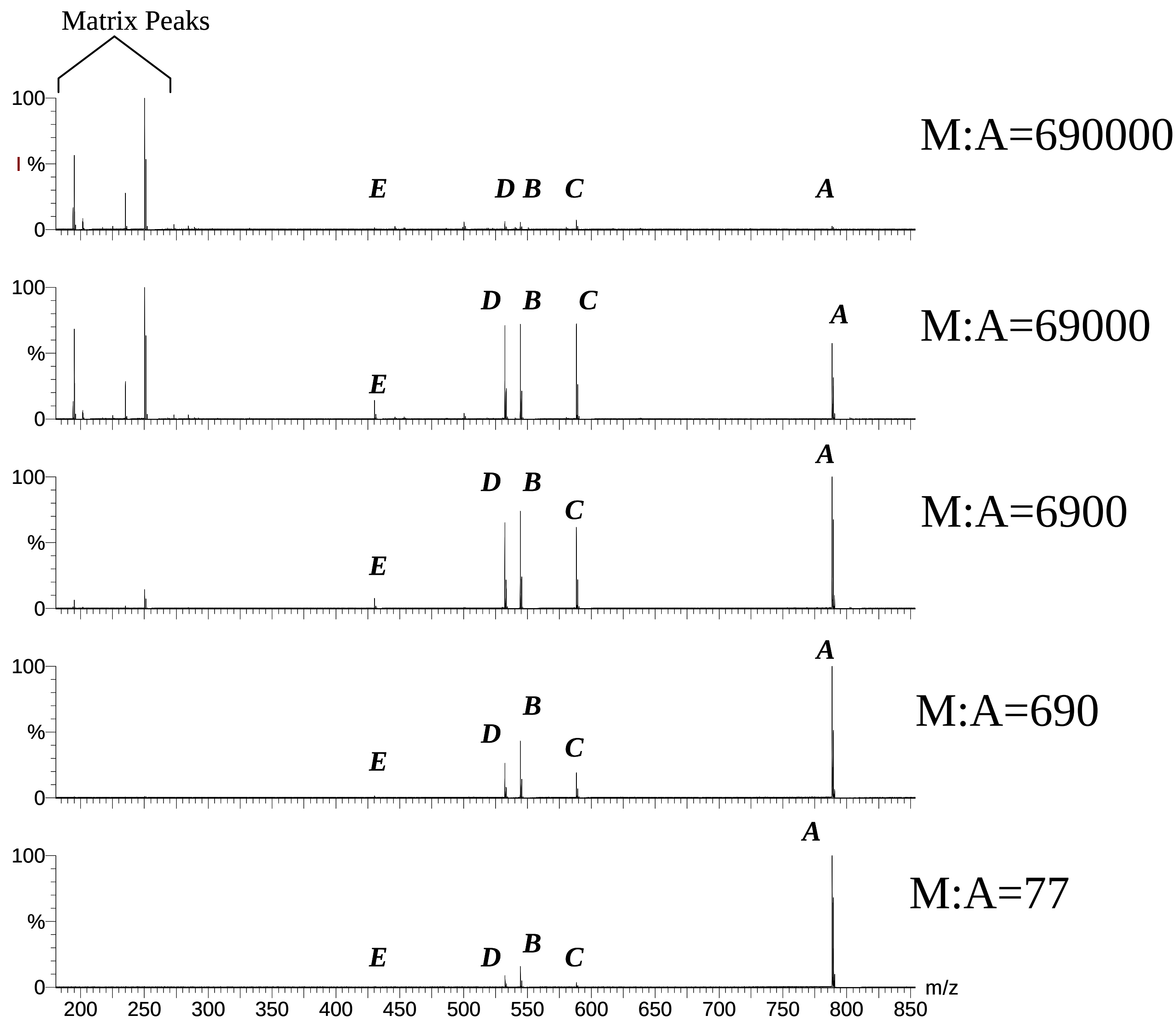
CAS#: 104751-29-9



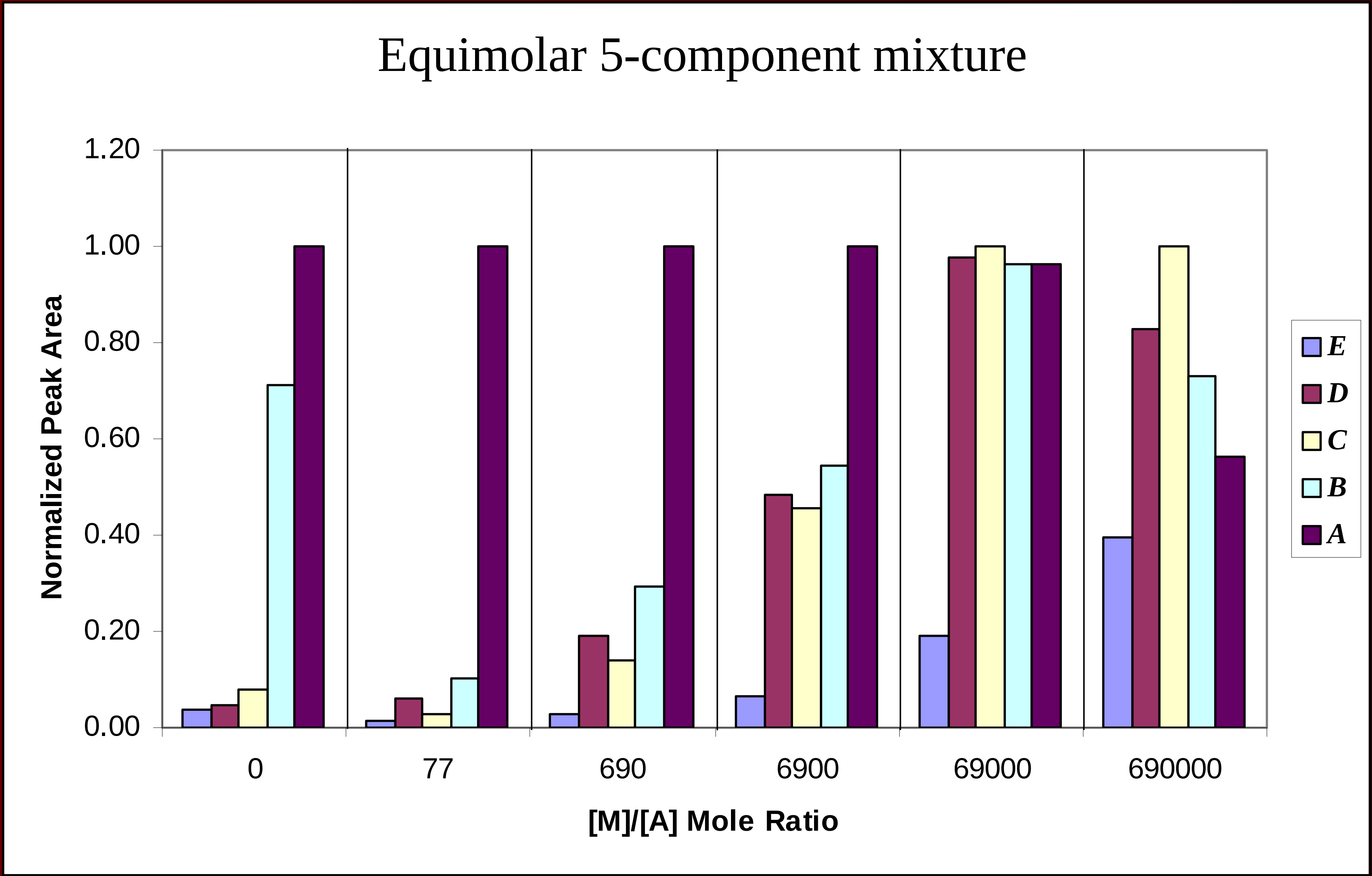
E

CAS#: 122648-99-1

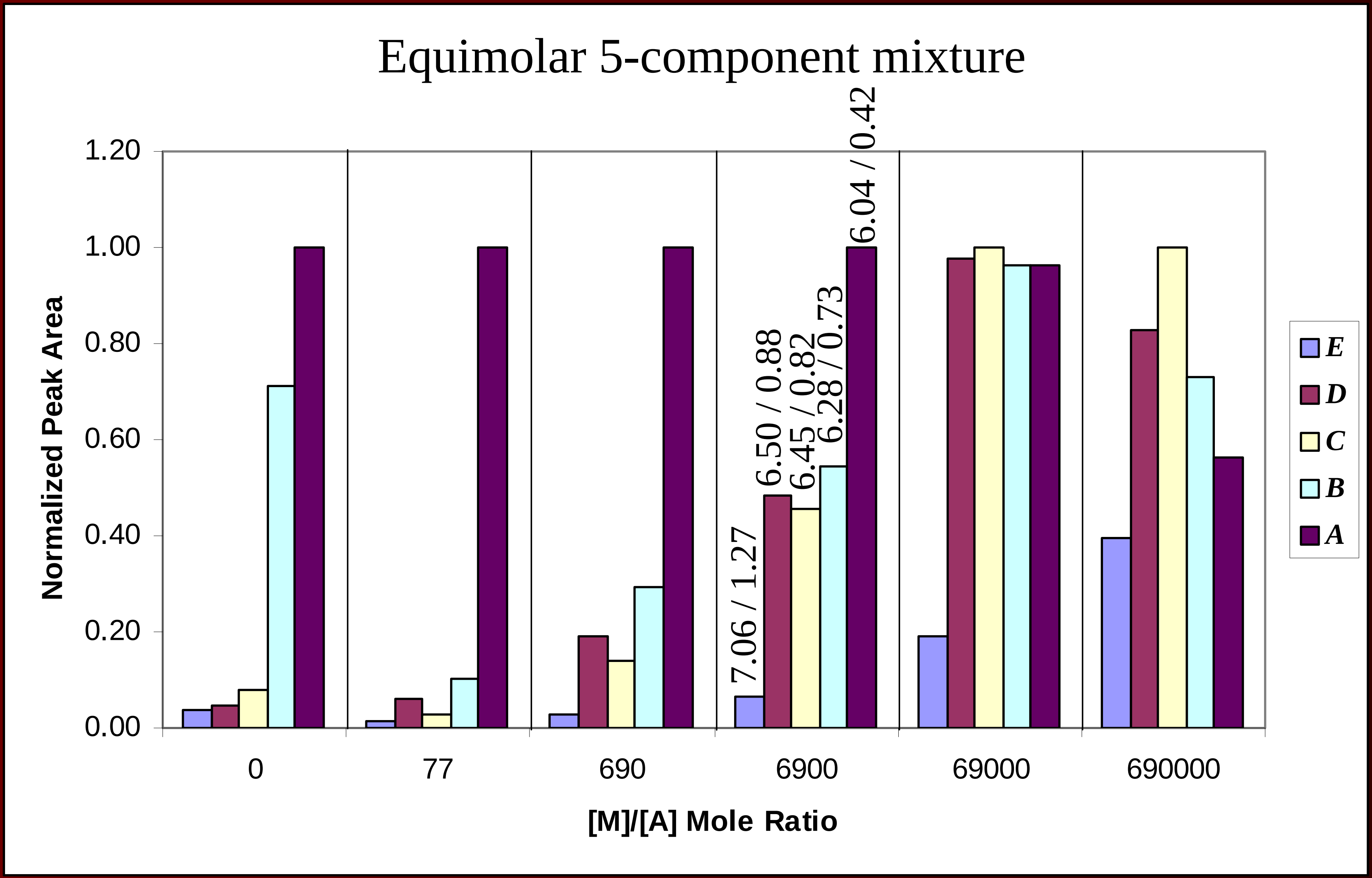
Electron Transfer MALDI



Electron Transfer MALDI



Electron Transfer MALDI



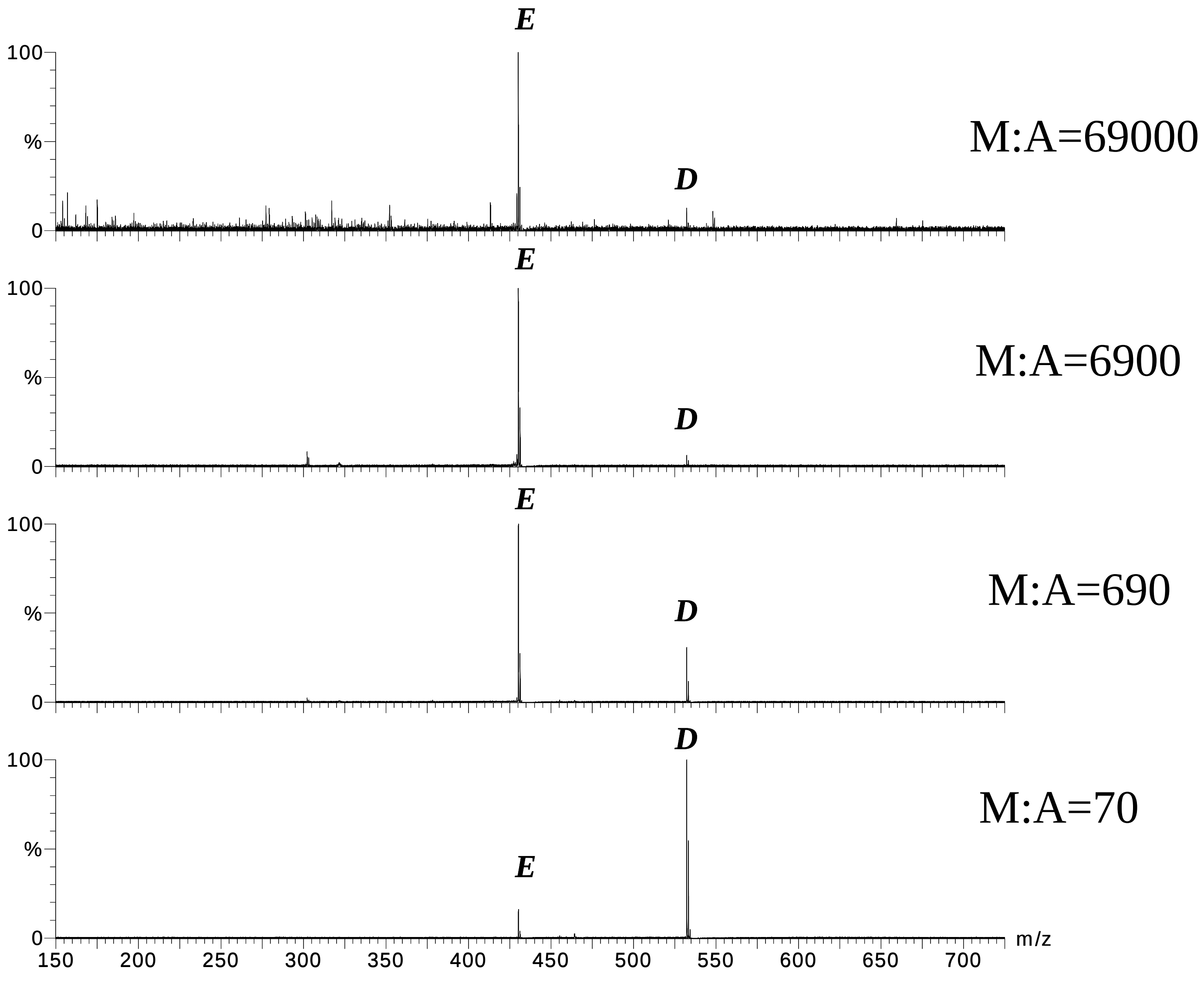
Electron Transfer MALDI

	IP (eV)	Eox (V)
Analyte A	6.04	0.423
Analyte B	6.28	0.728
Analyte C	6.45	0.820
Analyte D	6.50	0.884
Analyte E	7.06	1.273
DCTB	8.22	ca. 2.1

$M^+ + A \rightarrow M + A^+$

$A^+ + B \rightarrow A + B^+$

Electron Transfer MALDI



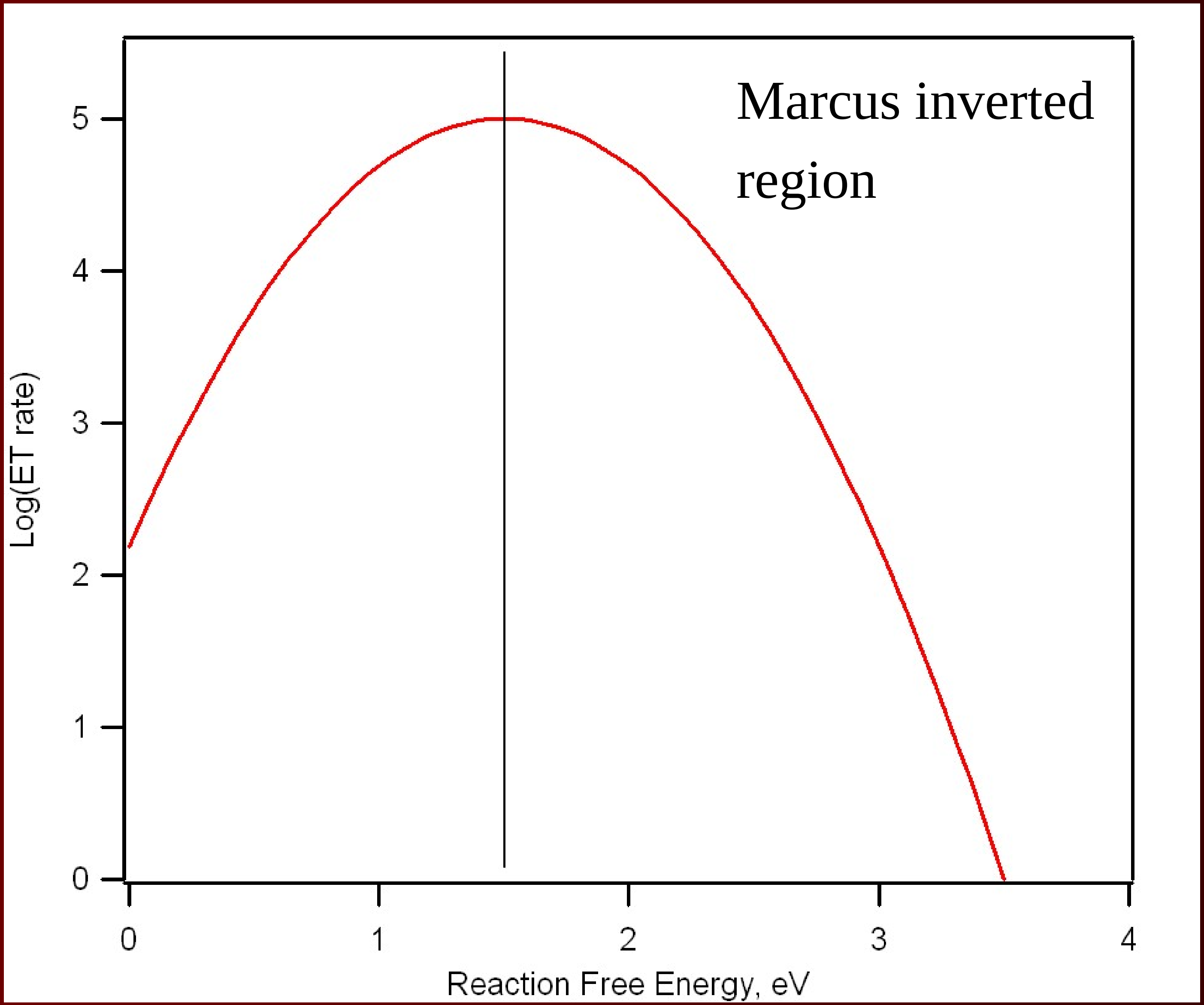
Electron Transfer MALDI

	IP (eV)	ΔIP (V)
Analyte D	6.50	3.13
Analyte E	7.06	2.57
nicotinic	9.63	

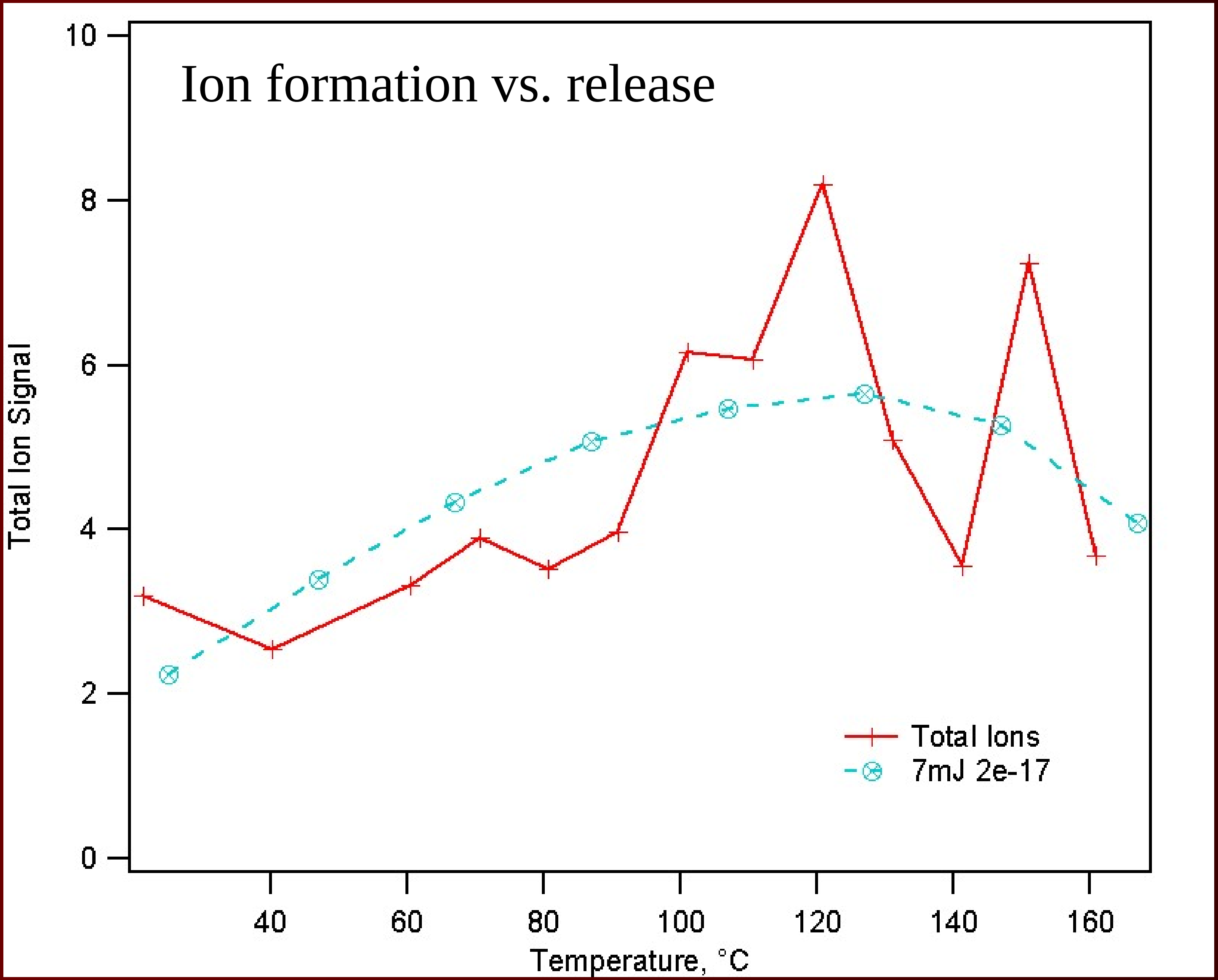
$M^+ + A \rightarrow M + A^+$

$(A^+ + B \rightarrow A + B^+)$

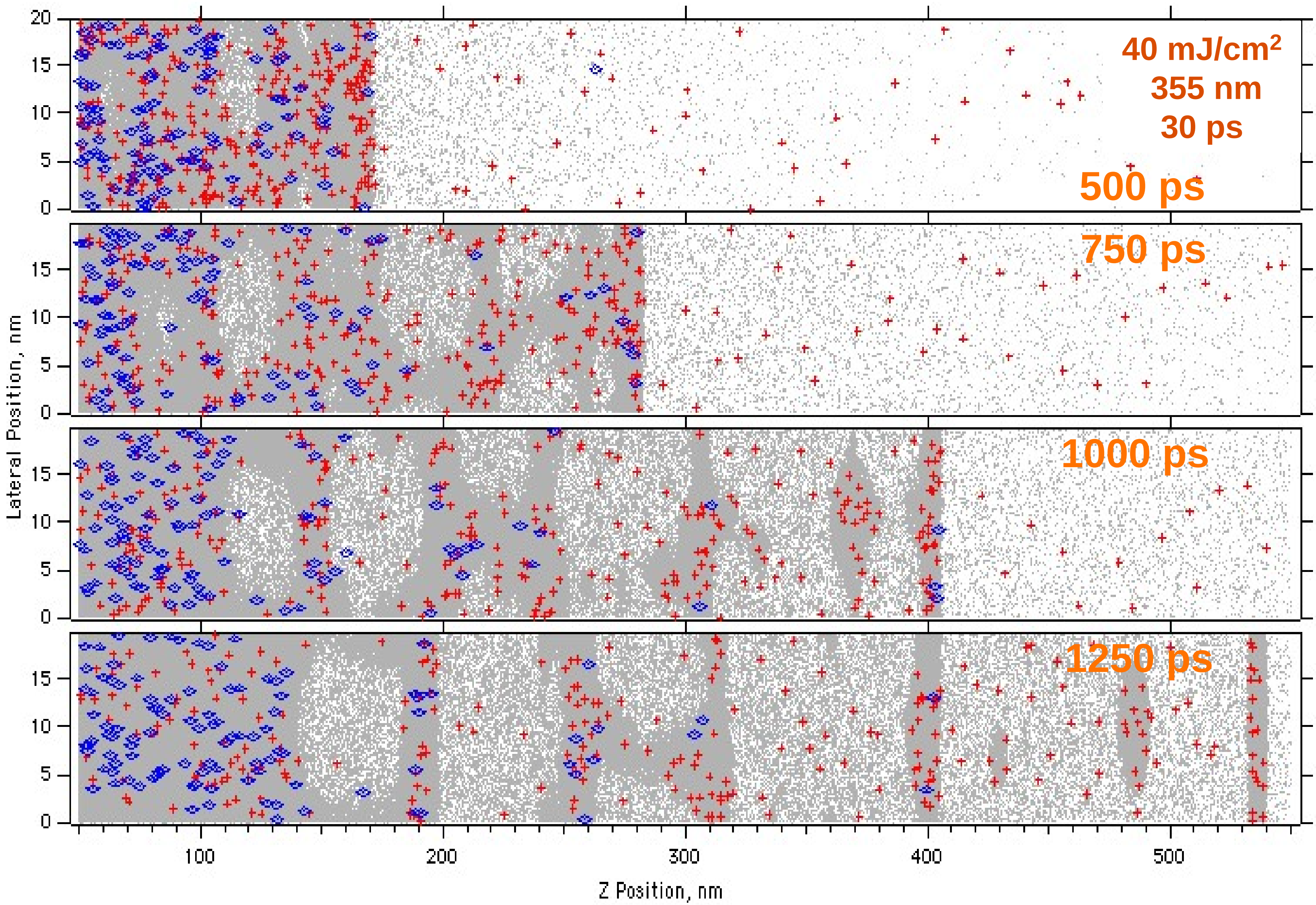
Electron Transfer MALDI



T Dependence of MALDI

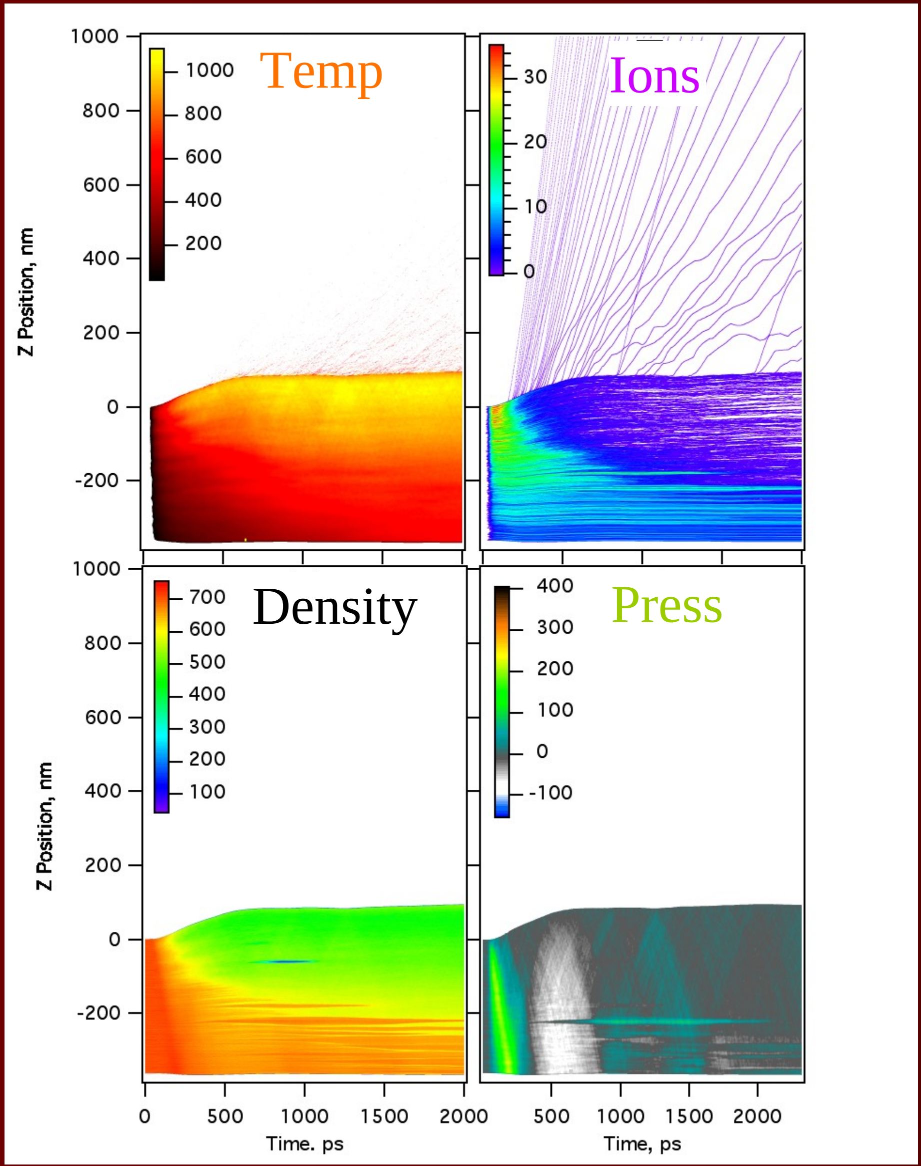


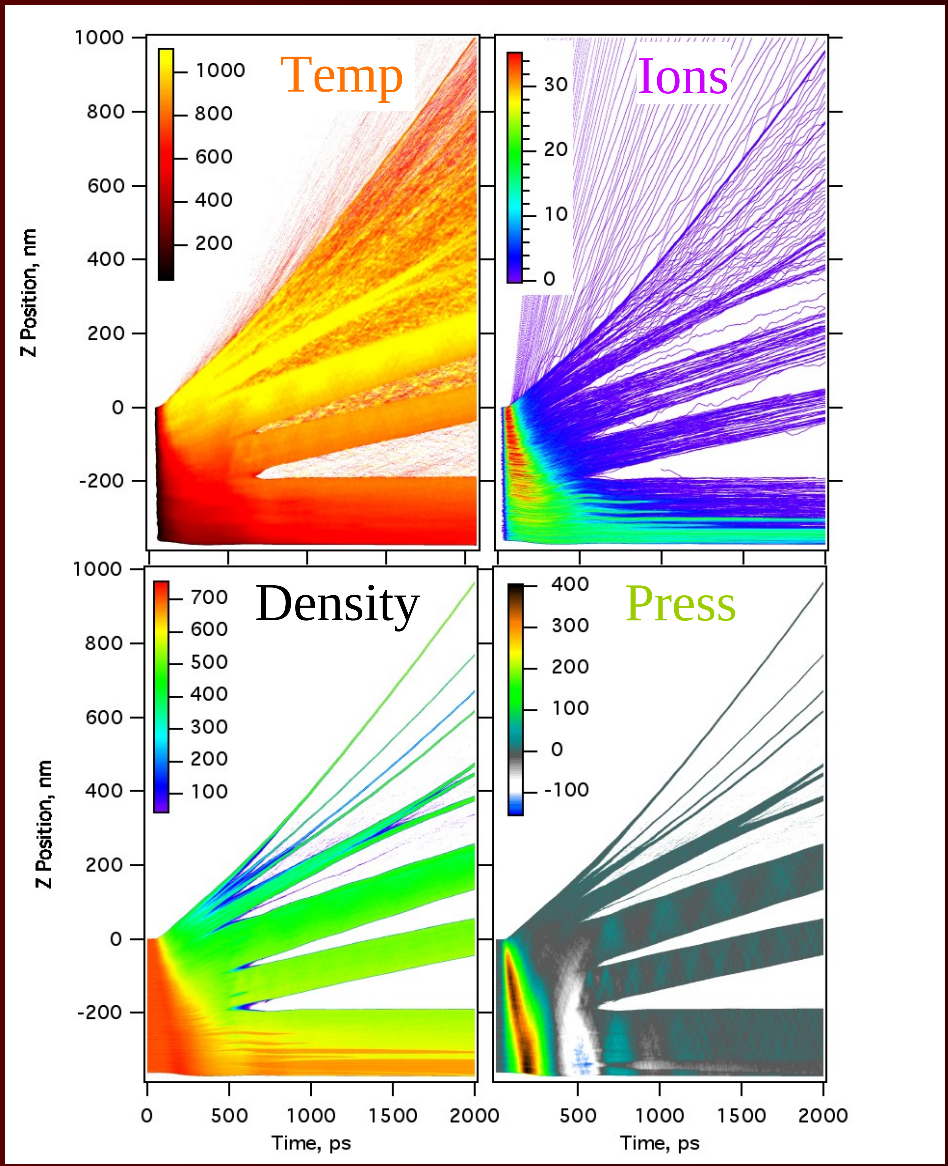
MALDI Ionization with MD



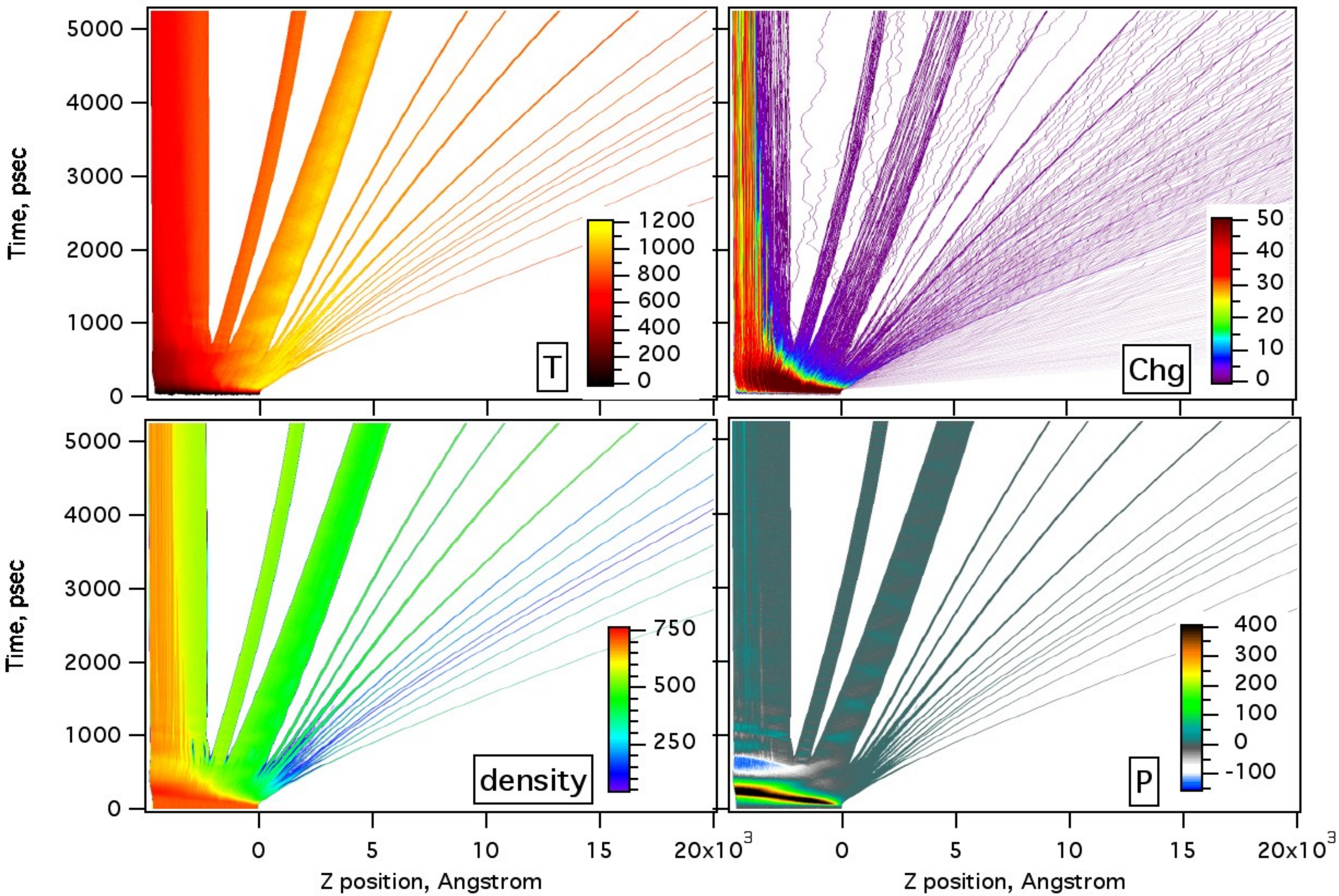
MALDI Ionizationby MD

MALDI Ionization with MD

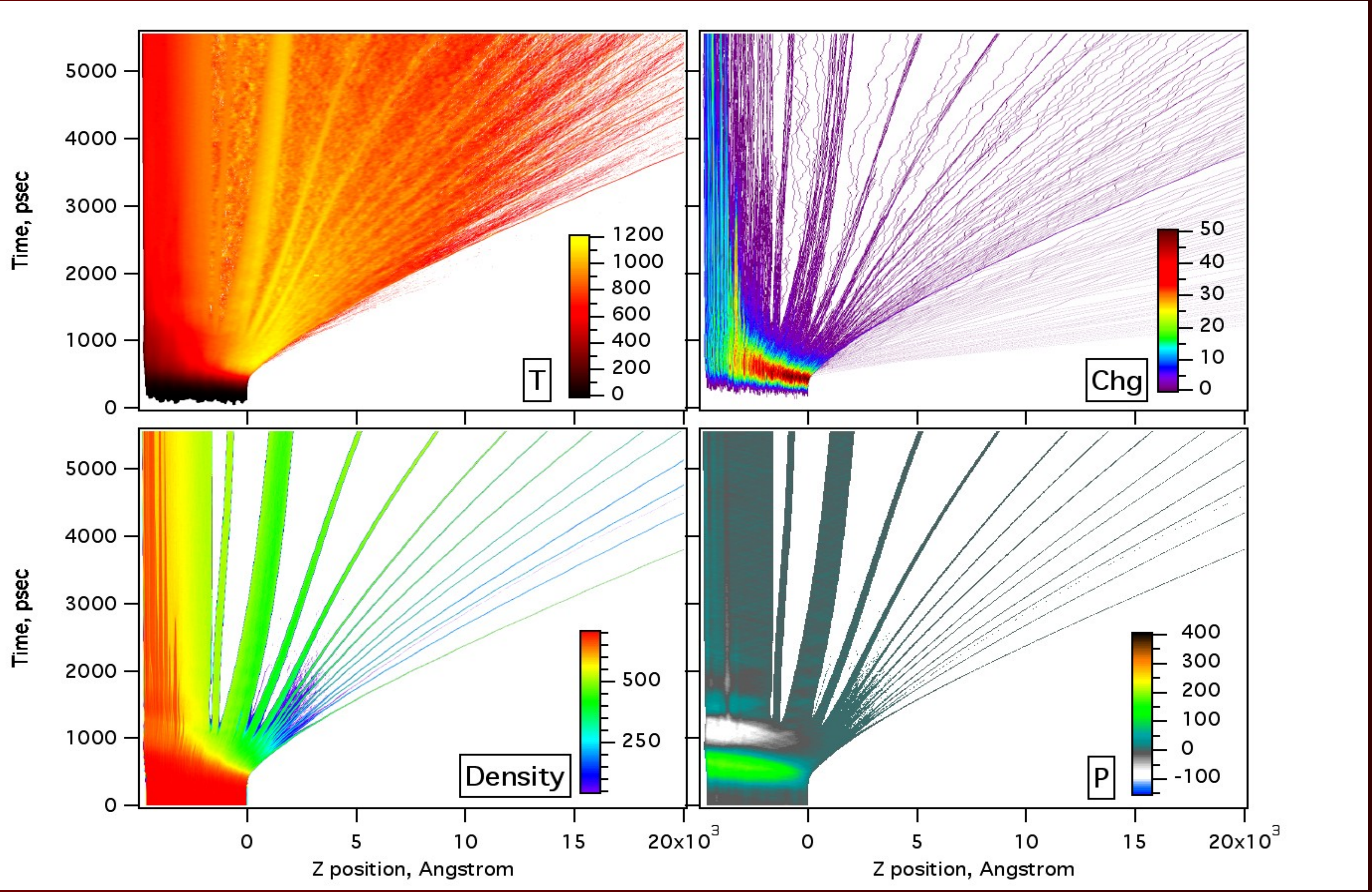




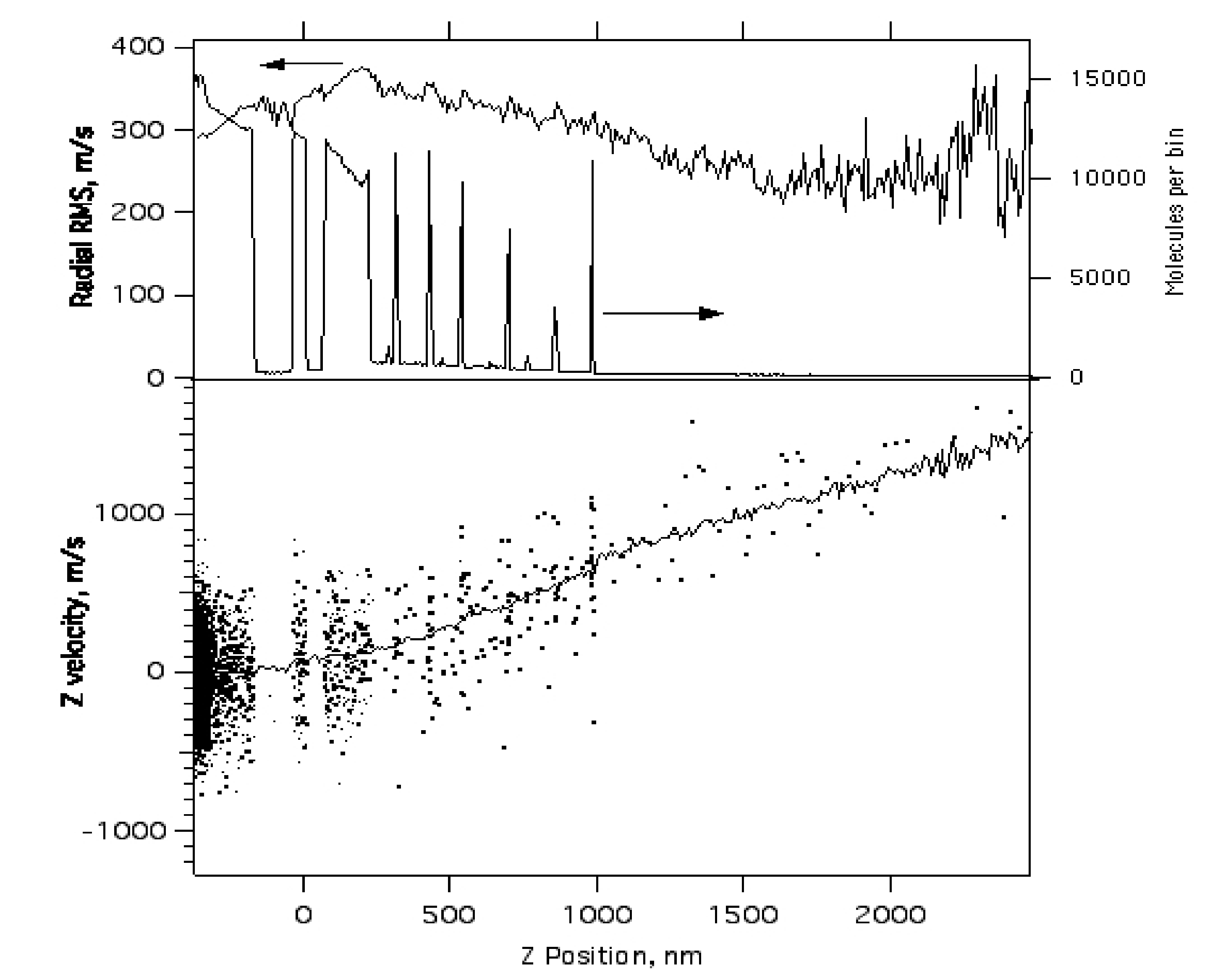
MALDI Ionizationby MD



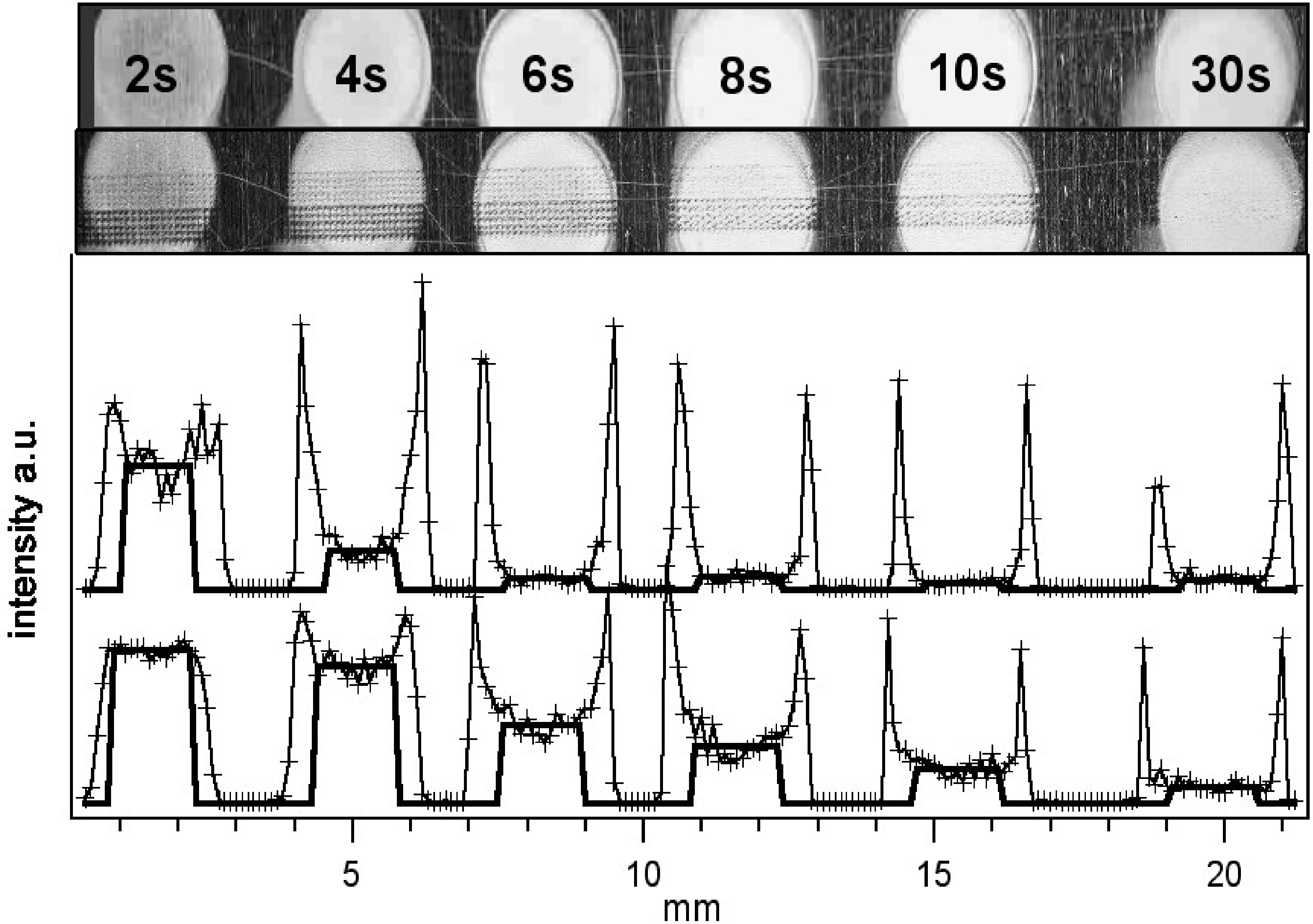
MALDI Ionizationby MD



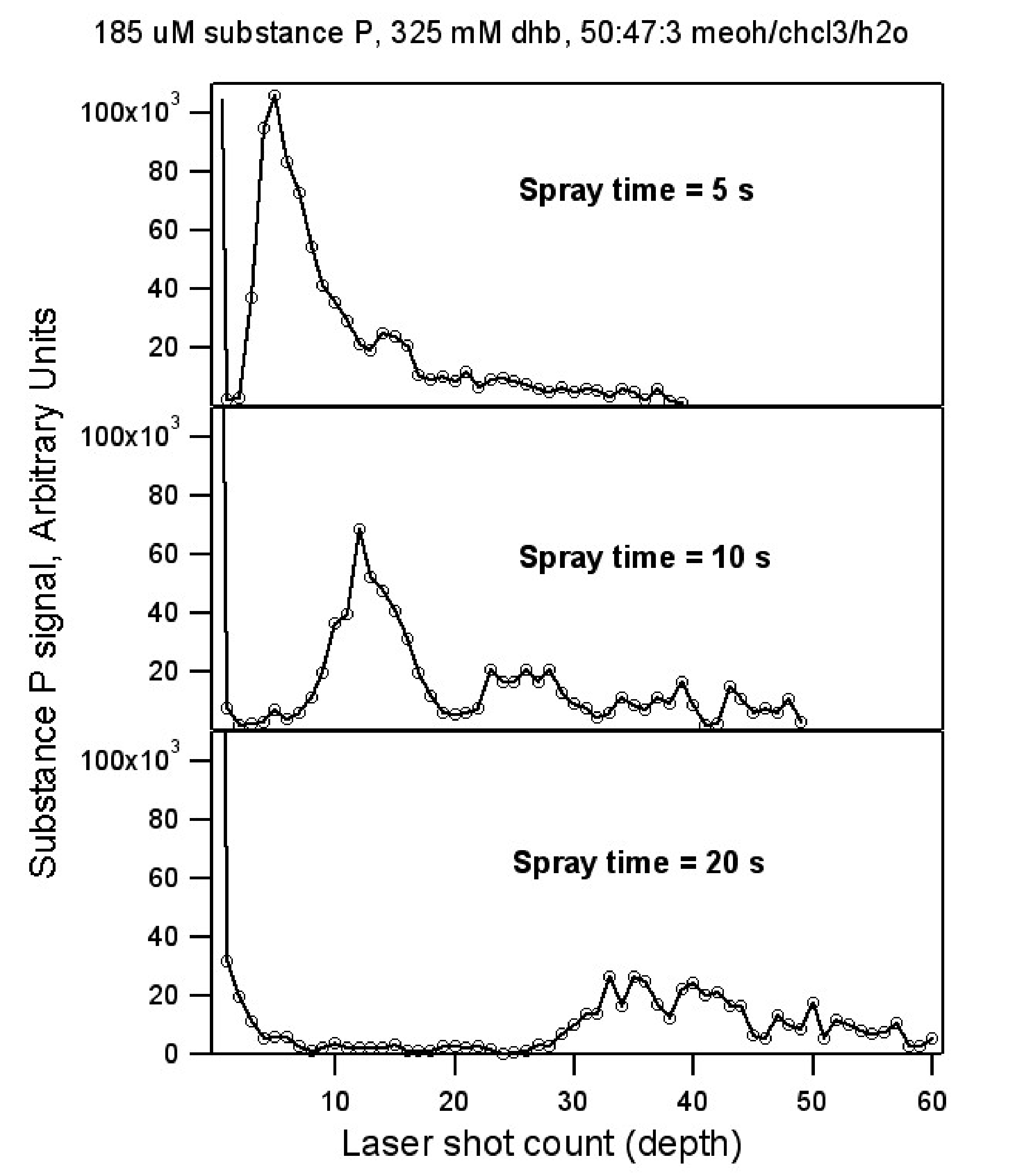
MALDI Ionizationby MD



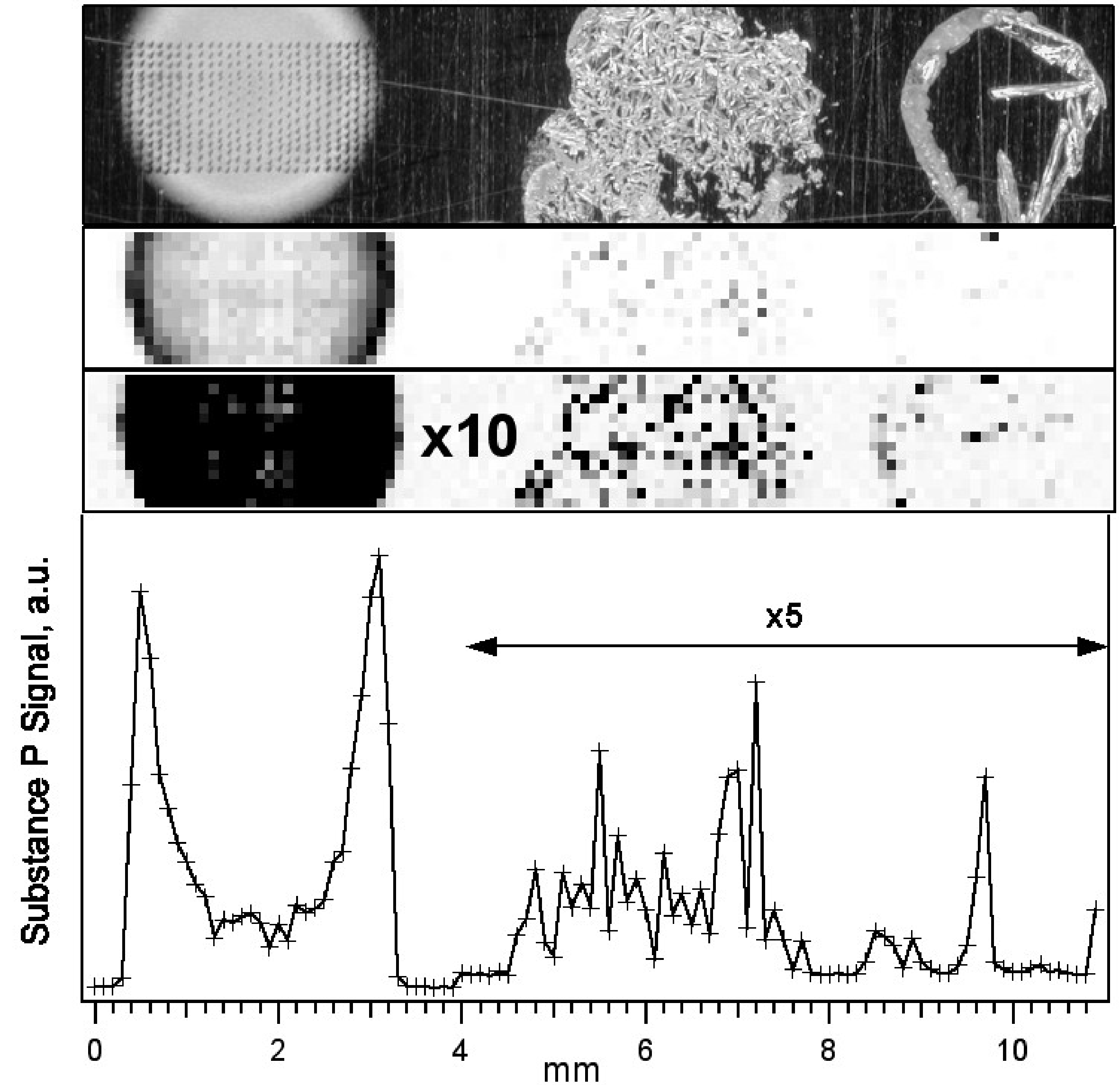
MALDI Sample Thickness



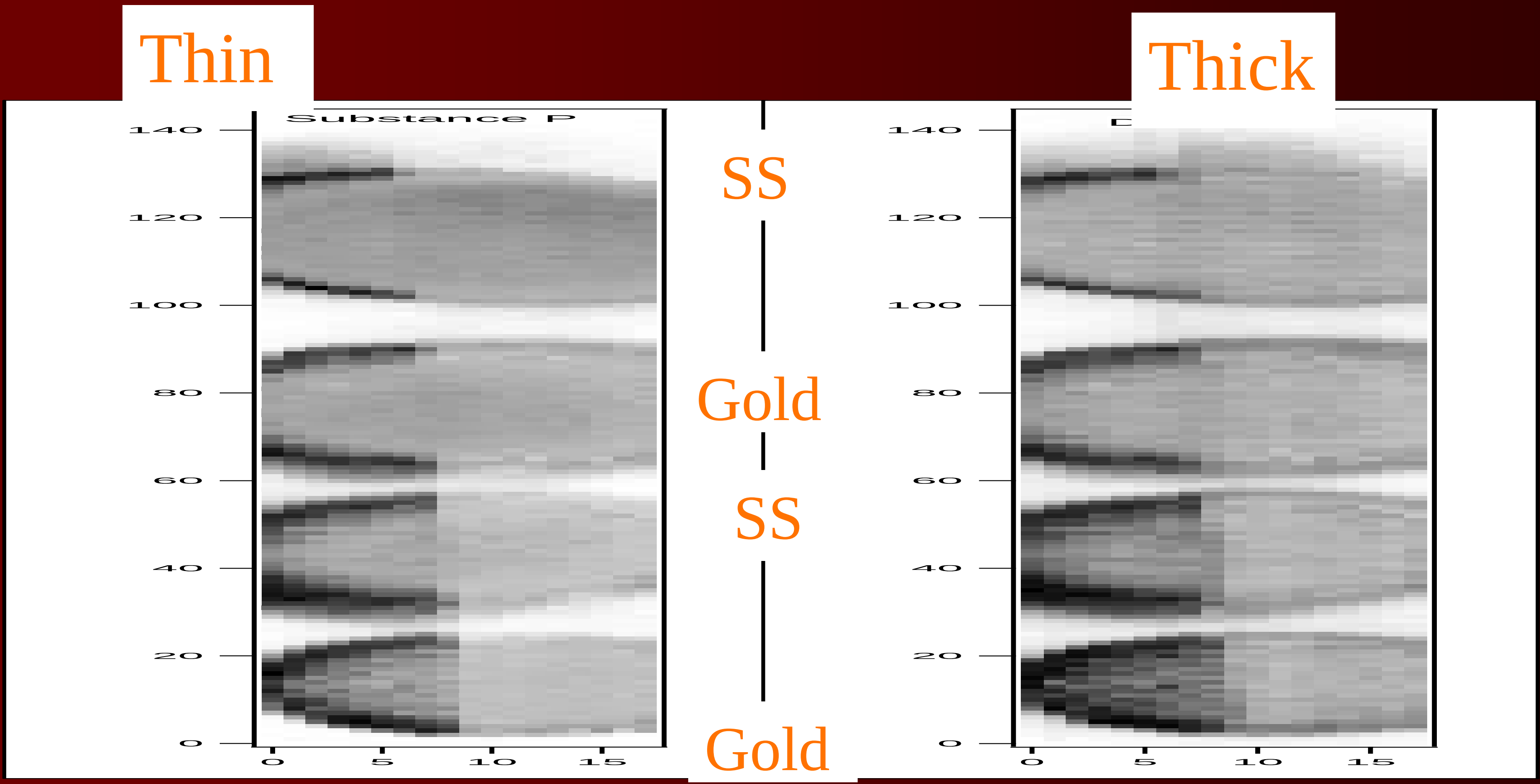
MALDI "Drilling"



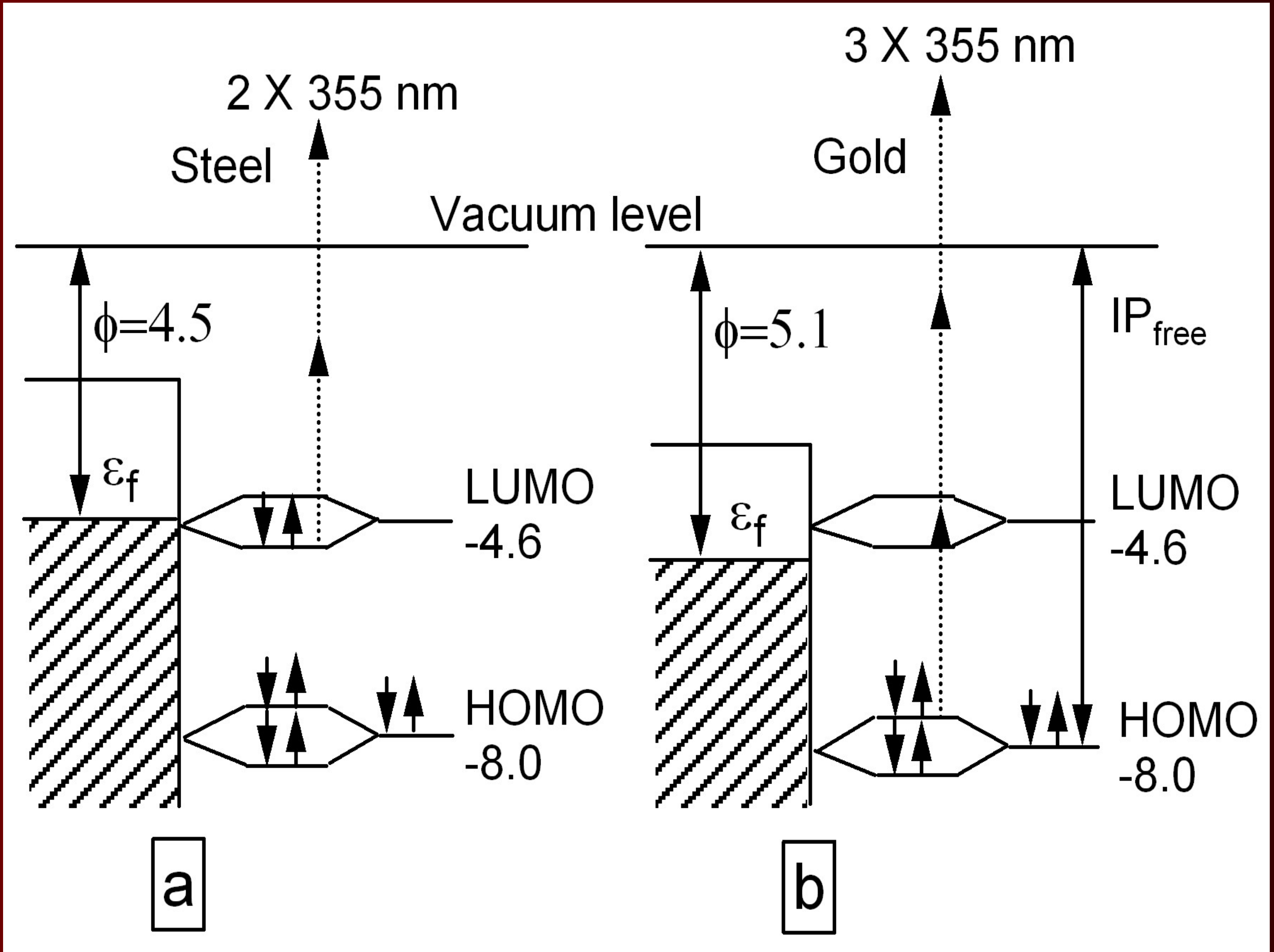
MALDI Sample Thickness



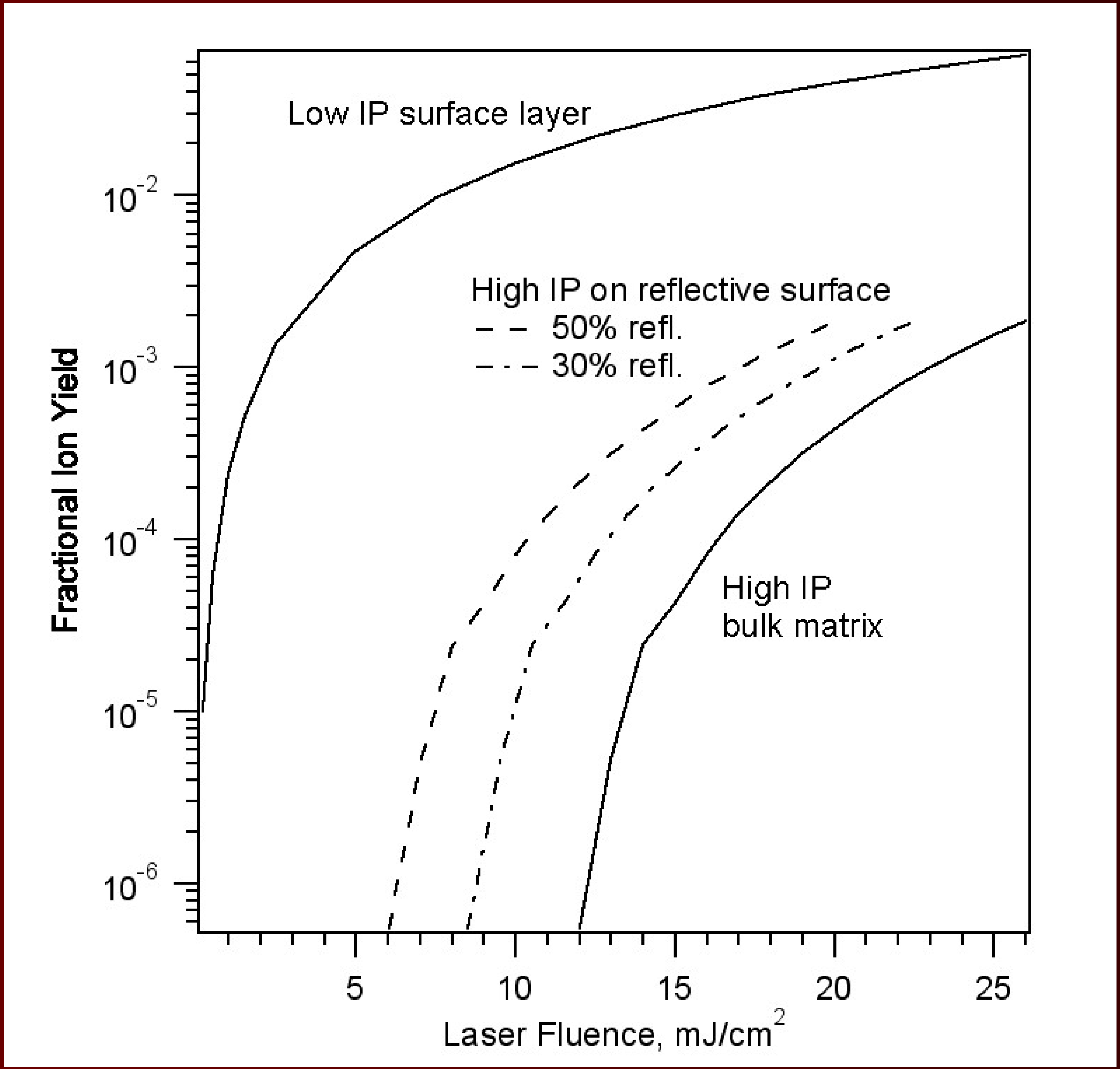
MALDI Substrate Type



MALDI Sample Thickness



MALDI Sample Thickness



Acknowledgments

ET MALDI

A. Hoteling, W. Nichols, D. Giessen, J. Lenhard

Temperature Dependence

W. Wallace, M. Arnould

MD sims

L. Zhigilei

Sample Thickness

G. McCombie, M. Stöckli

Continuum model : msi.stoeckli.net/technology/maldimodel.htm

Questions: rich@maldi.ms

MALDI model via web

msi.stoeckli.net/technology/maldimodel.htm

MALDI > MSI > Interest > Group

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Two-step MALDI Ionization Model

Calculate matrix and 1 or 2 analyte ion yields using the model of:
Journal of Mass Spectrometry v. 37, p. 867 (2002) and
Analytical Chemistry v. 75, p. 2199 (2003)

This model assumes:
Matrix ions are created by excitation pooling reactions (step 1, primary ionization)
Analyte ions are created by charge transfer reactions with matrix ions (step 2, secondary ionization)
The ablation plume is dense, so classical thermodynamics and kinetics describe the system

The default matrix parameters are for 2,5 dihydroxybenzoic acid, the best studied matrix.

If you do not enter a value in a field, the <*default*> will be used.

Your results will be emailed to the following address (typically requires 1 day):

Email for results: [ ]

Click this button to submit the parameters: [Calculate MALDI ionization]

Basic Parameters

Laser:

Wavelength (nm)<355>: 355
(consider also the S_0-S_1 cross section below, if you change this)
Pulse width (sec) <5e-9>: 5e-9

Fluence (mJ/cm^2) <15>: 15
Spot size (mm, typ. 0.1-0.5) <0.1>: 0.1
Two pulses? (•) Off ( ) On
Pulse delay (sec) <1e-9>: 1e-9
Scale factor for second pulse <1>: 1

Analyte Ion Formation*:
Analyte 1:

Relative concentration (0-1) <0>: 0
Molecular weight (Da) <1000>: 1000

Theory: the next step

Strengths of current model:

- Based on established physics + chemistry
- Parameters (increasingly) known
- Encompasses whole MALDI process
- Computationally tractable
- Gives excellent correlation with experiment

Weaknesses of current model:

Plume description still approximate:

$T_{sublimation}$ a poor description of evaporation

Very early expansion probably not jet-like

Limited ability to treat ablative ejection

Solution:

Use molecular dynamics to model early times.

Major Remaining Limitations

Step function vaporization:

Even with the shortest laser pulses, the sample heats on a ns time scale => desorption/ablation is not a sudden event.

During heating, there may be a transition from evaporative desorption to spallation-like ablation.

Adiabatic Expansion:

Requires local equilibrium, which may not hold at short times for short laser pulses. (already a correction in model)

MALDI Ionizationby MD

"Breathing Sphere" model of Zhigilei and Garrison:

- Molecules = spheres with one internal motion
- Allows interconversion of internal + kinetic energy
- Relatively fast for MD

MD vs. Continuum Model

- Rate equations -> probabilities.
- Requires mechanistic interpretation!
  e.g. pooling probability vs. distance.
- Limited temporal and spatial extent: e.g.
  10 X 10 X 36 nm, few ns.

Intermolecular Processes: Neutral Molecules

Ground electronic state (S_0):

Morse potential...

Excited electronic states (S_1, Sn):

dipole-dipole => $1/R^6$

collisional decay

pooling

exciton hopping

Short range (neighbors), with periodic boundary conditions

Intermolecular processes: Ions

Primary ion generation mechanism:

$S_1 + S_n$ pooling

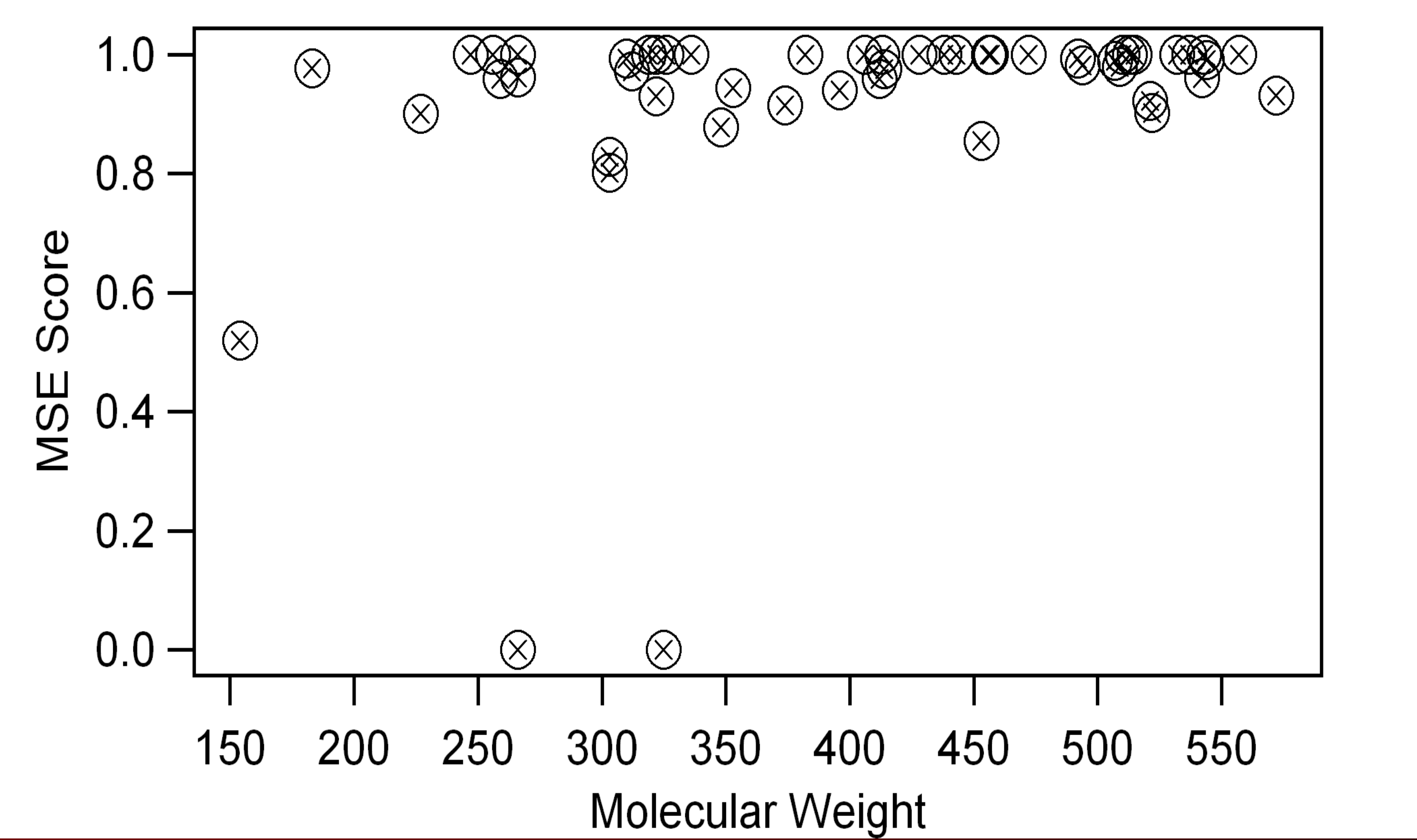
Ionization => low energy electrons

- random direction
- propagate until absorbed or escapes vertically
- cross section from Asfandiarov, et al.

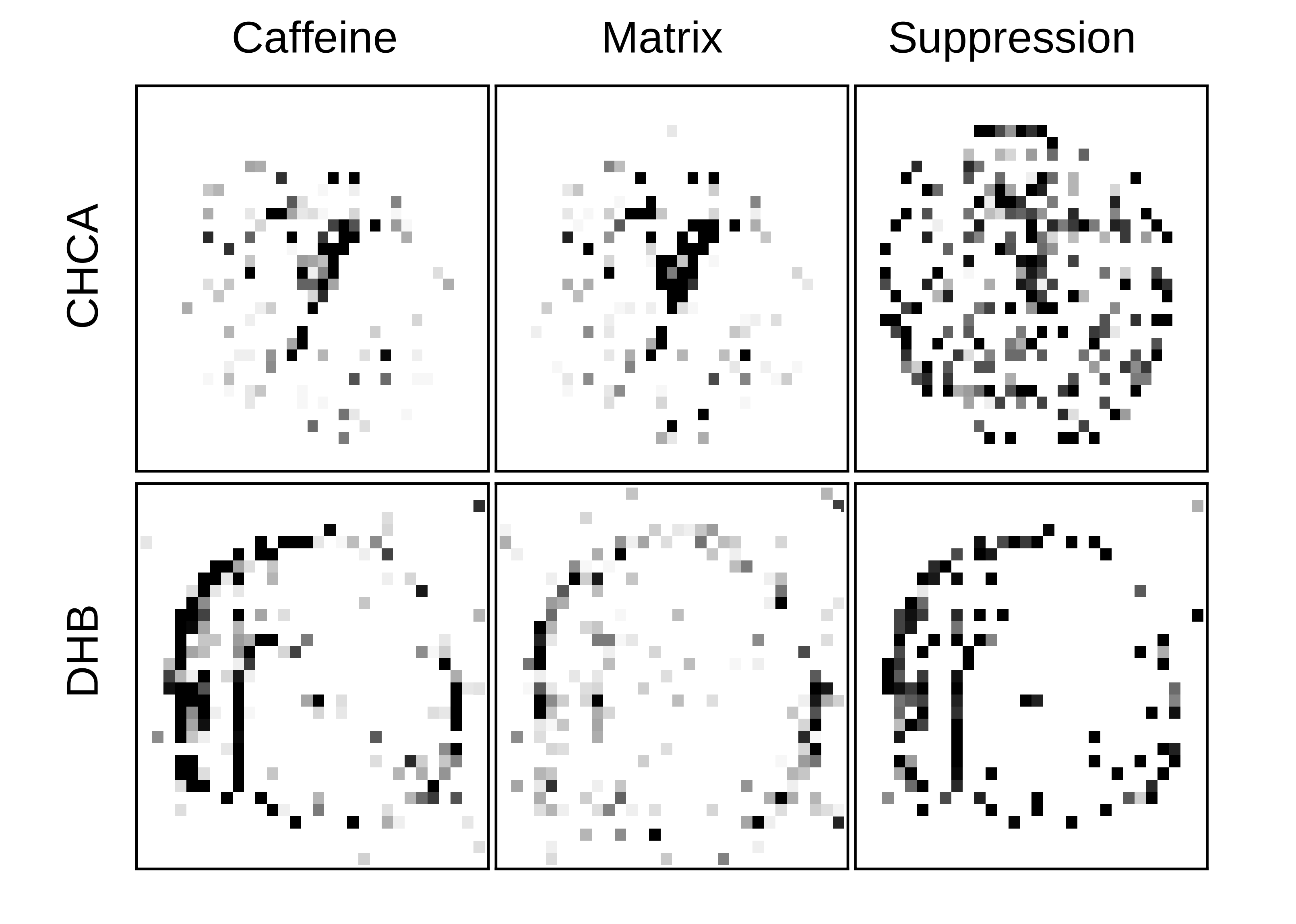
Coulomb forces are long range:

Summed over all ions, with replicated cell on all sides.

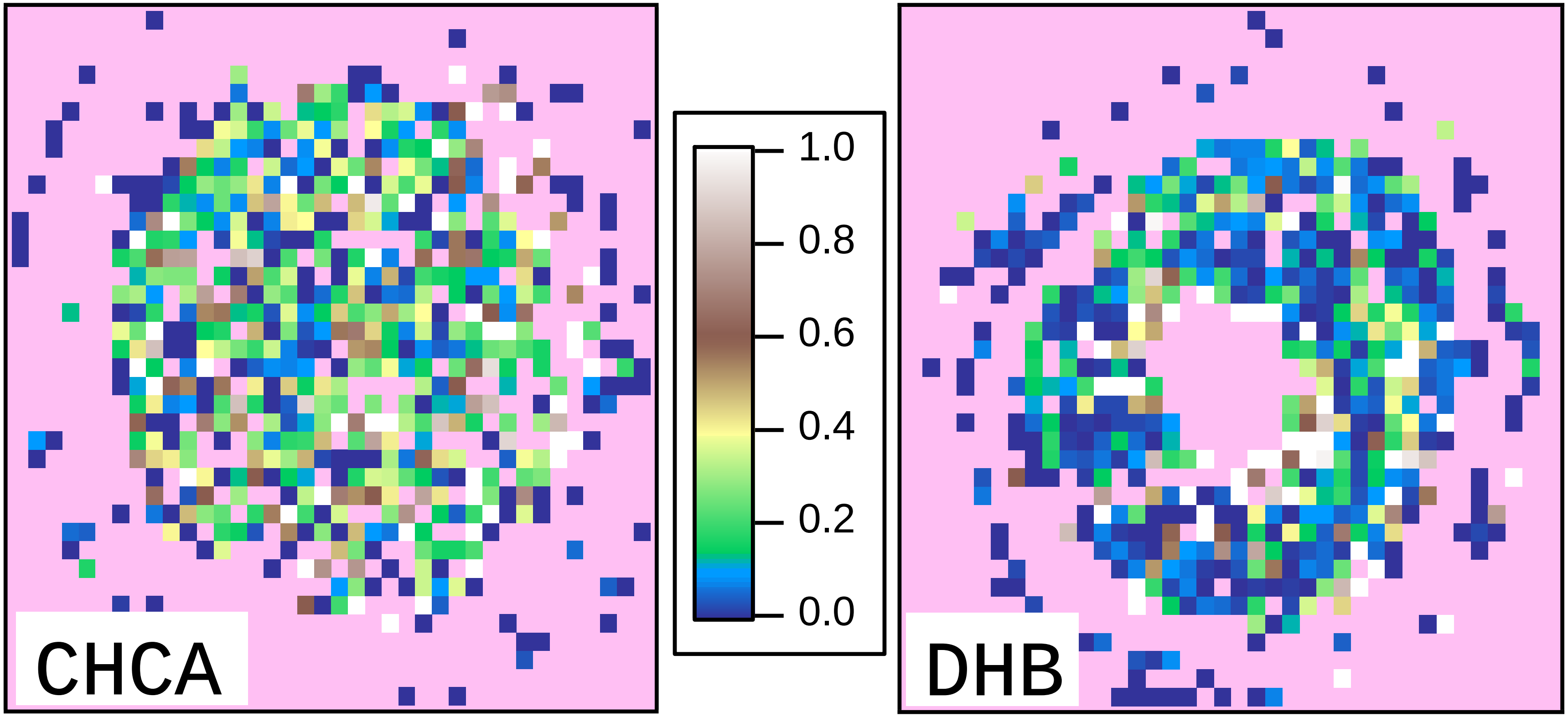
MSE Generality



MSE Characteristics

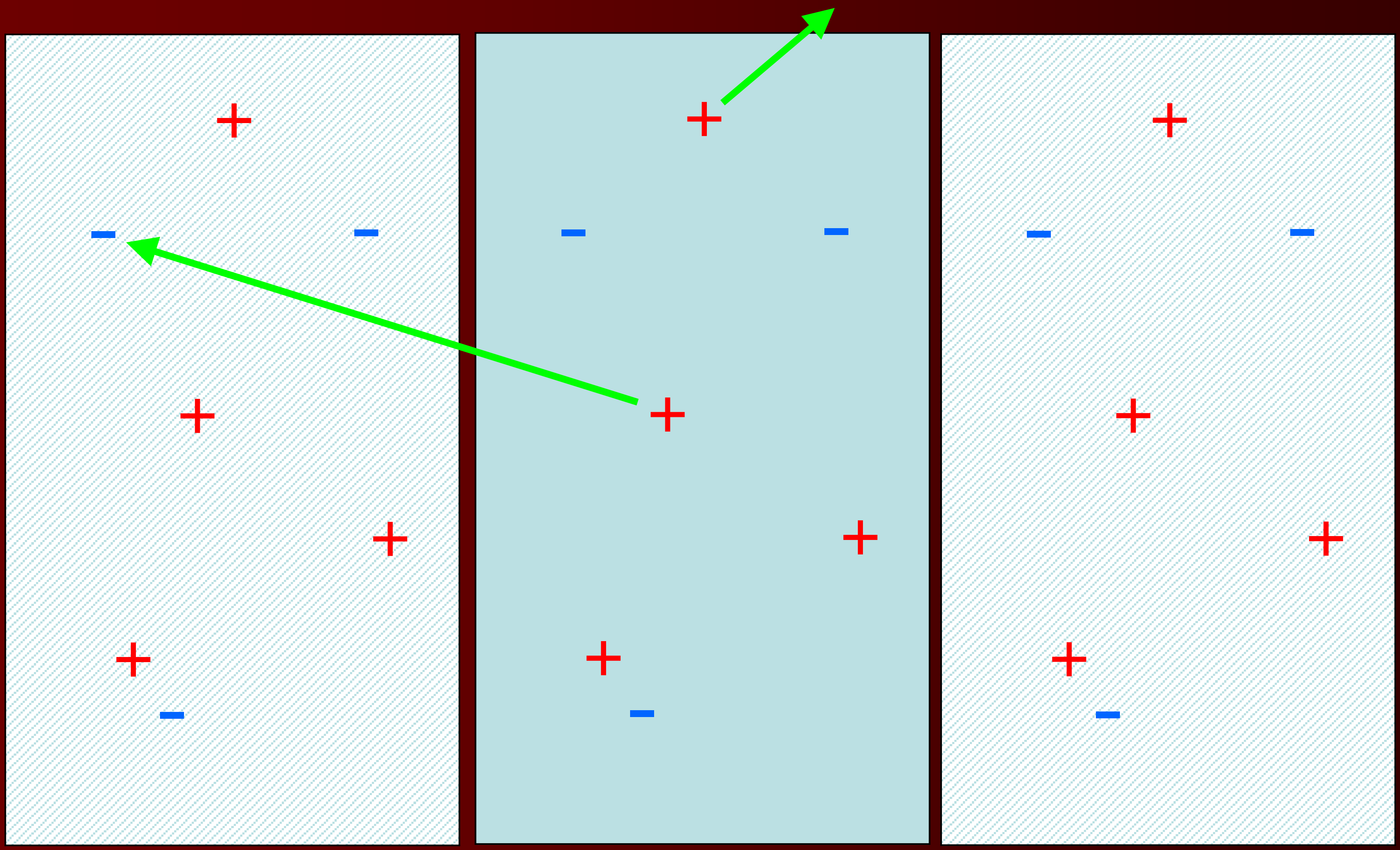


MSE with 2 analytes

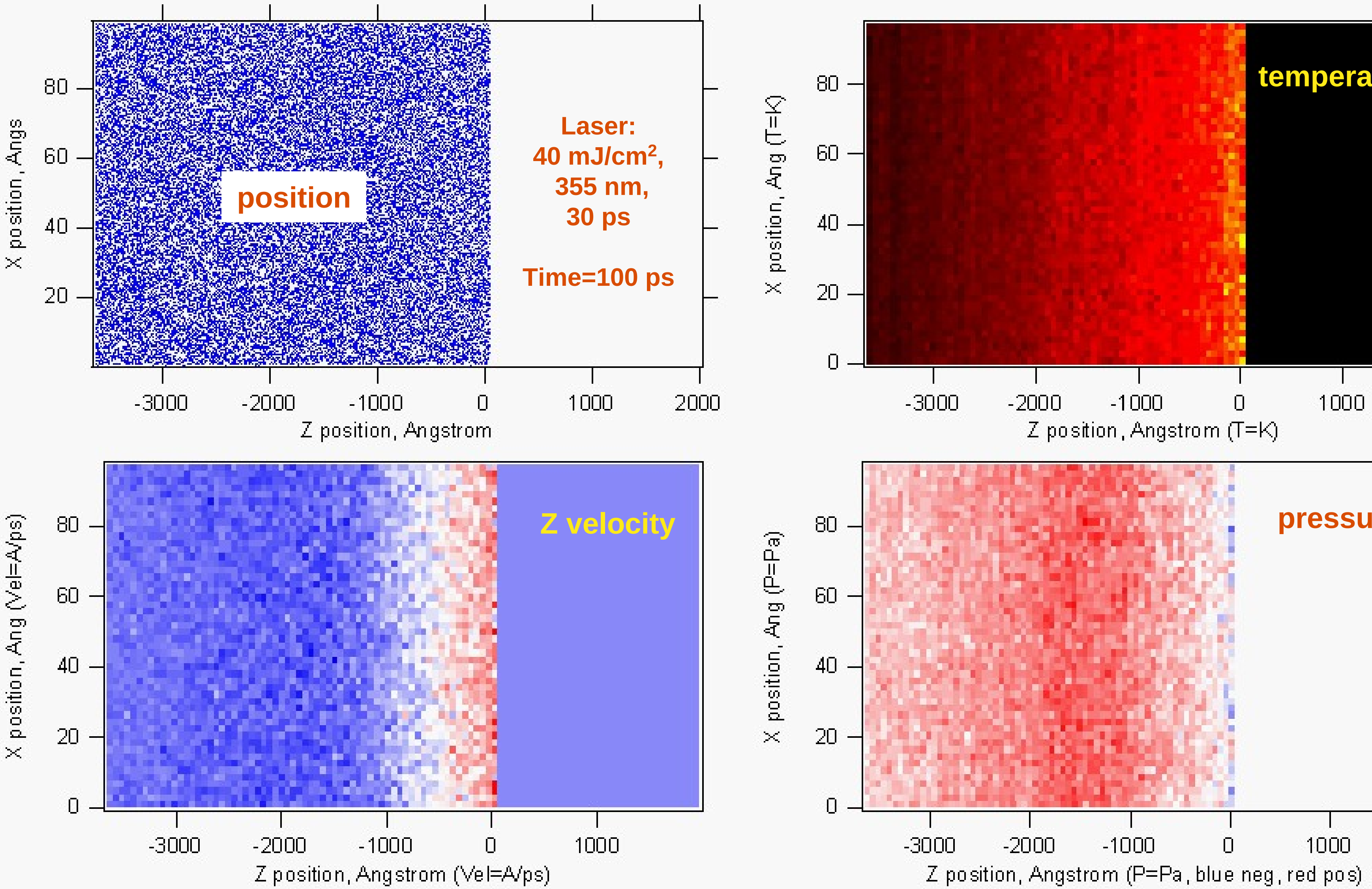


Expected A:B ratio (0.25)=Green

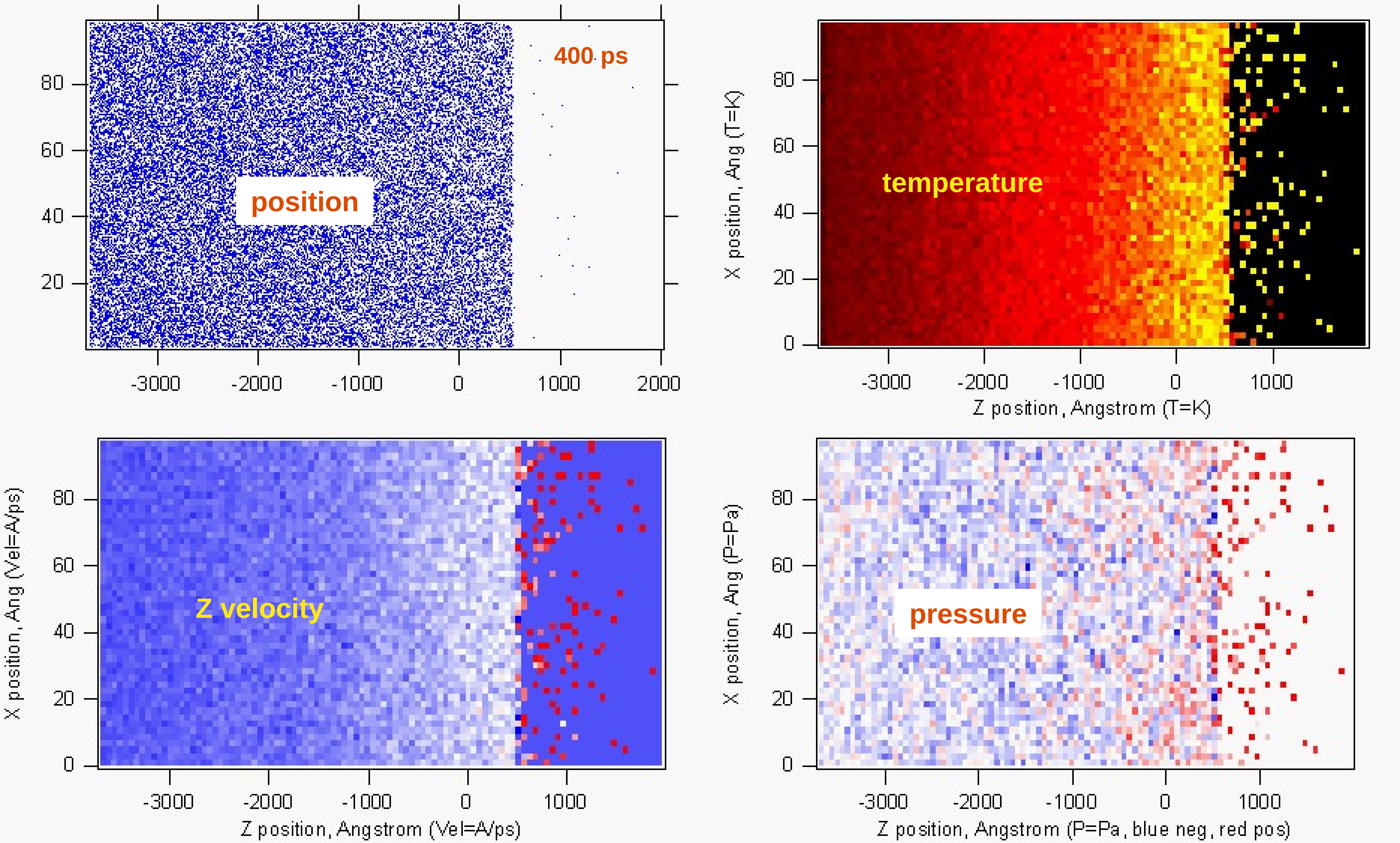
Intermolecular processes: Electrons and Ions



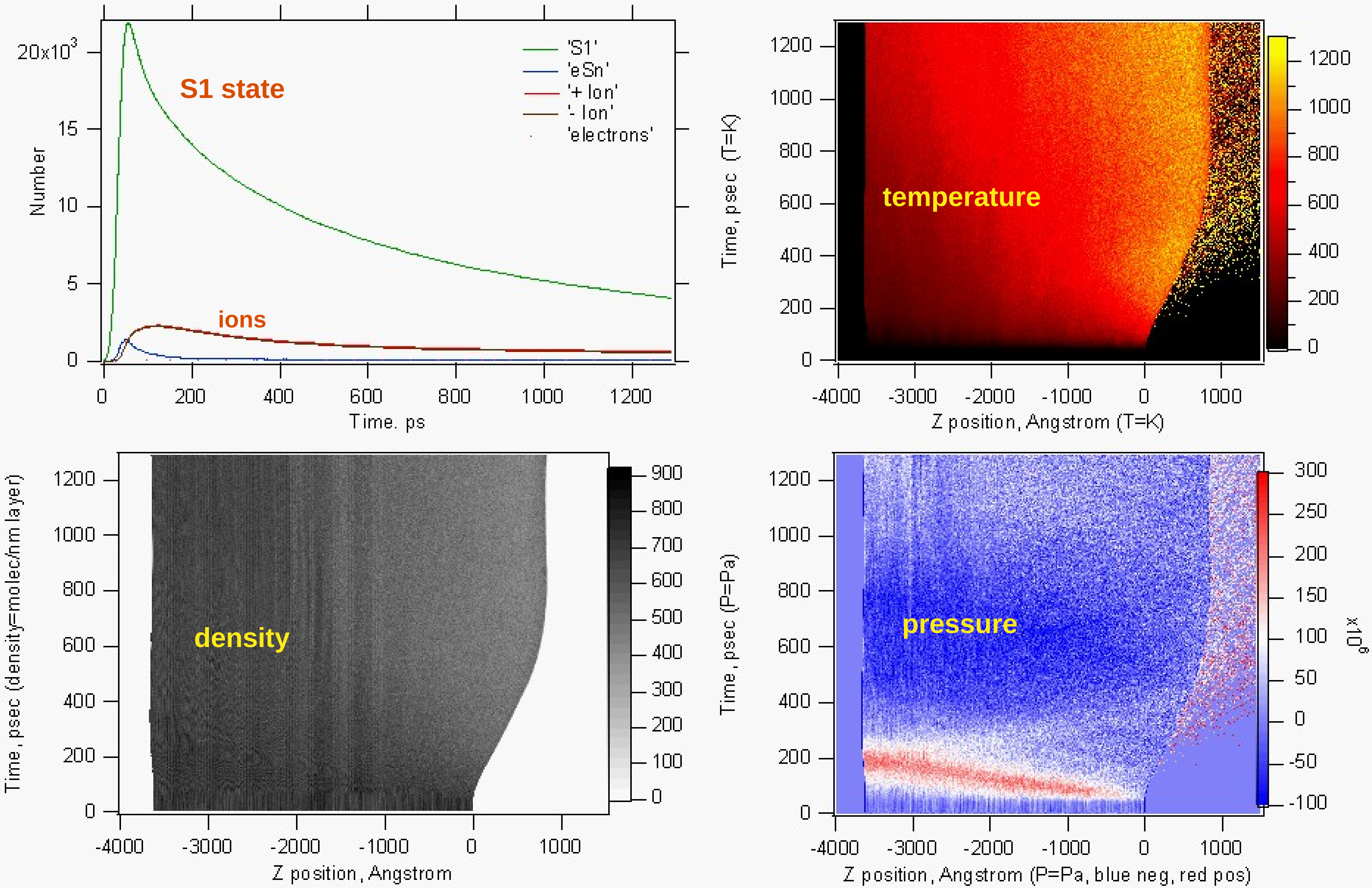
MALDI Ionization with MD



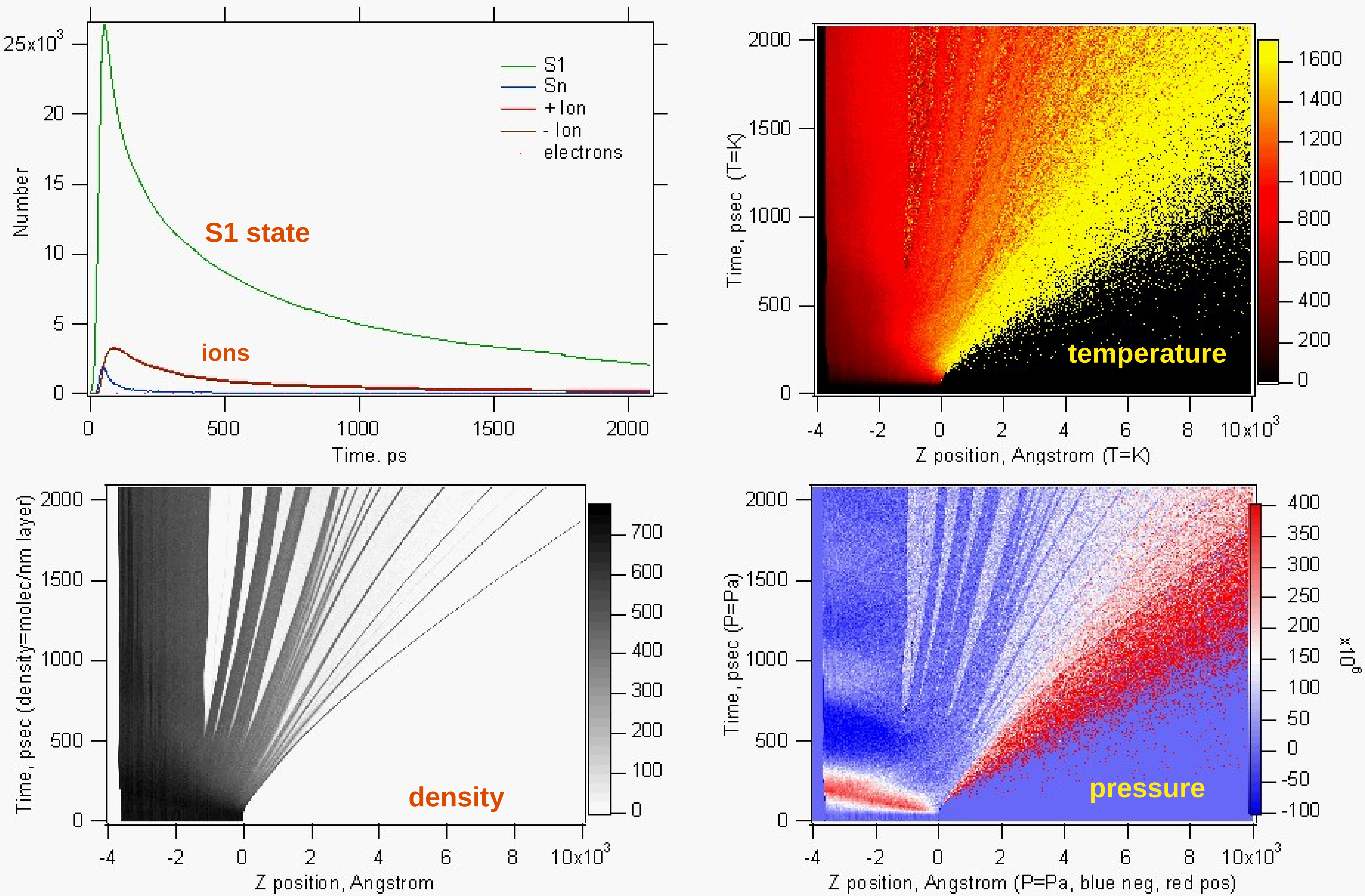
MALDI Ionization with MD



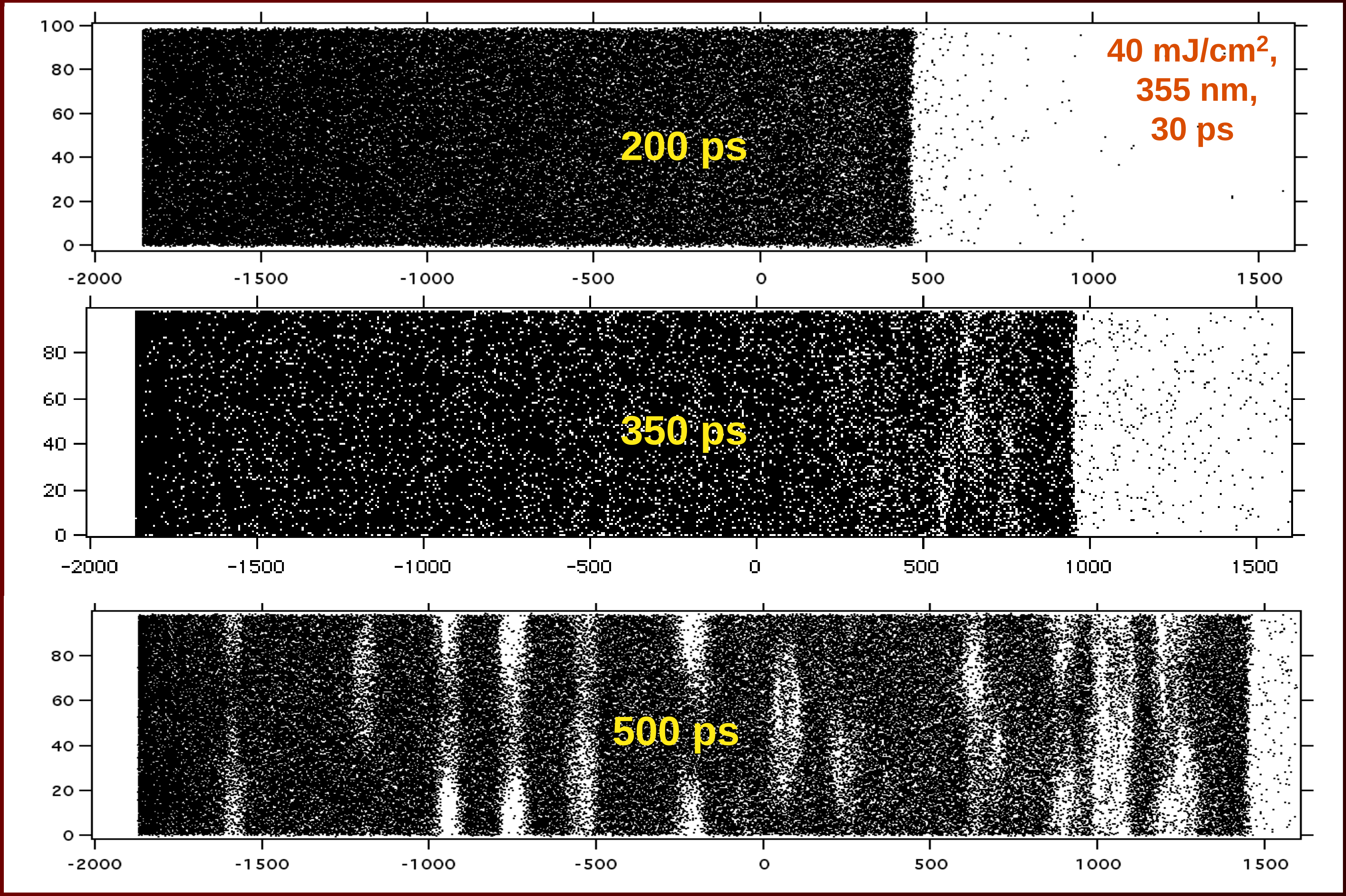
MALDI Ionization with MD



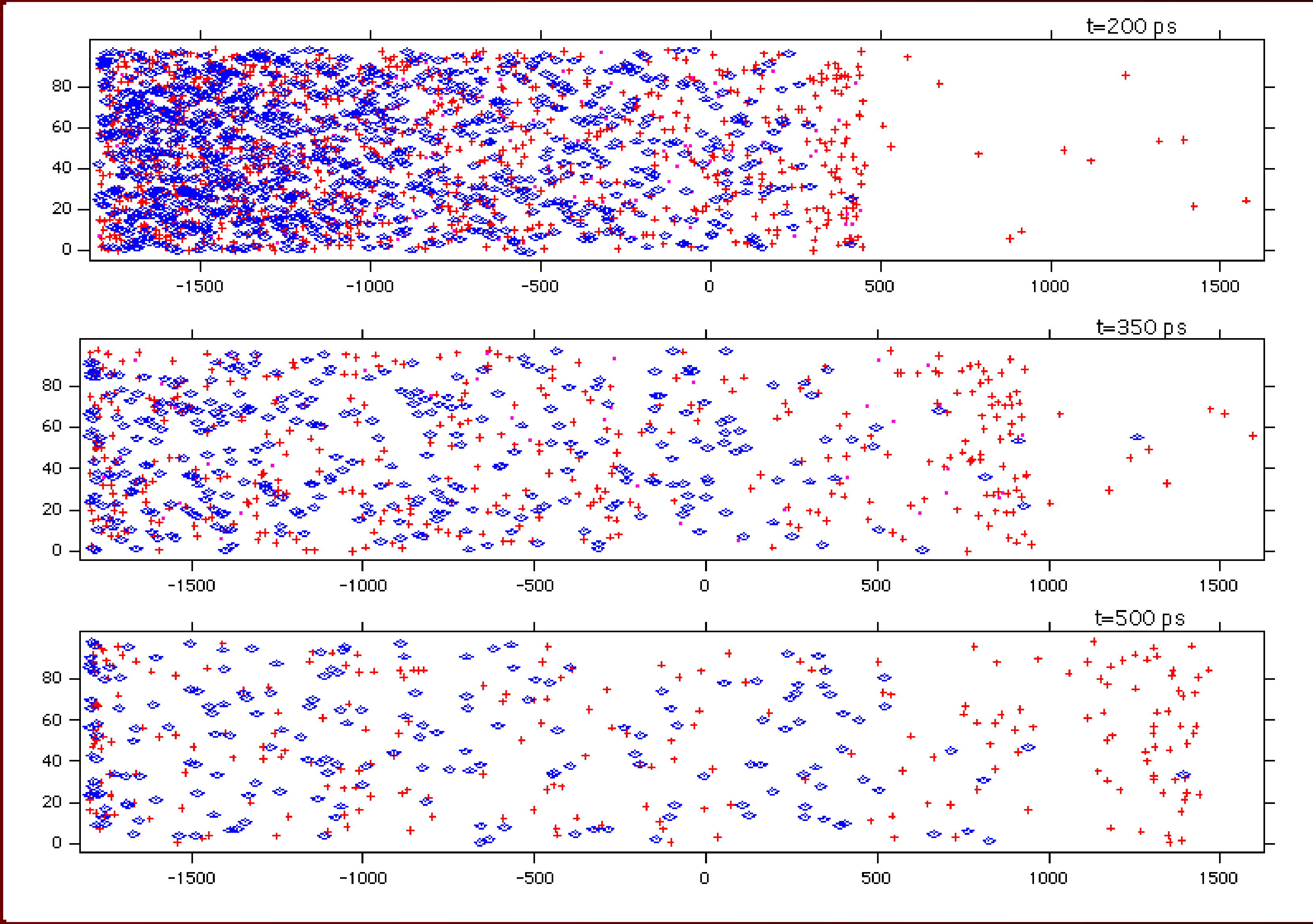
MALDI Ionization with MD



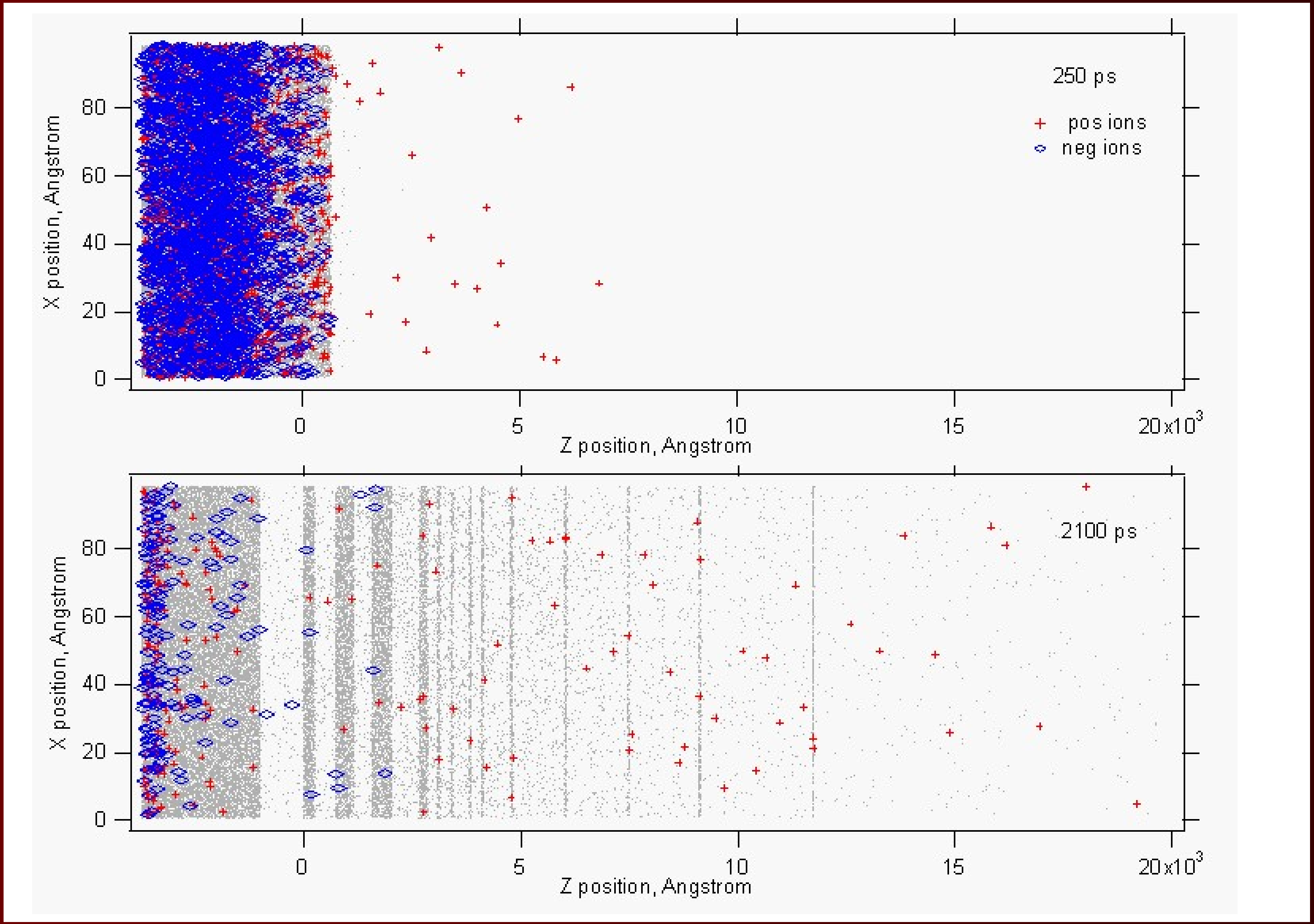
MALDI Ionization with MD



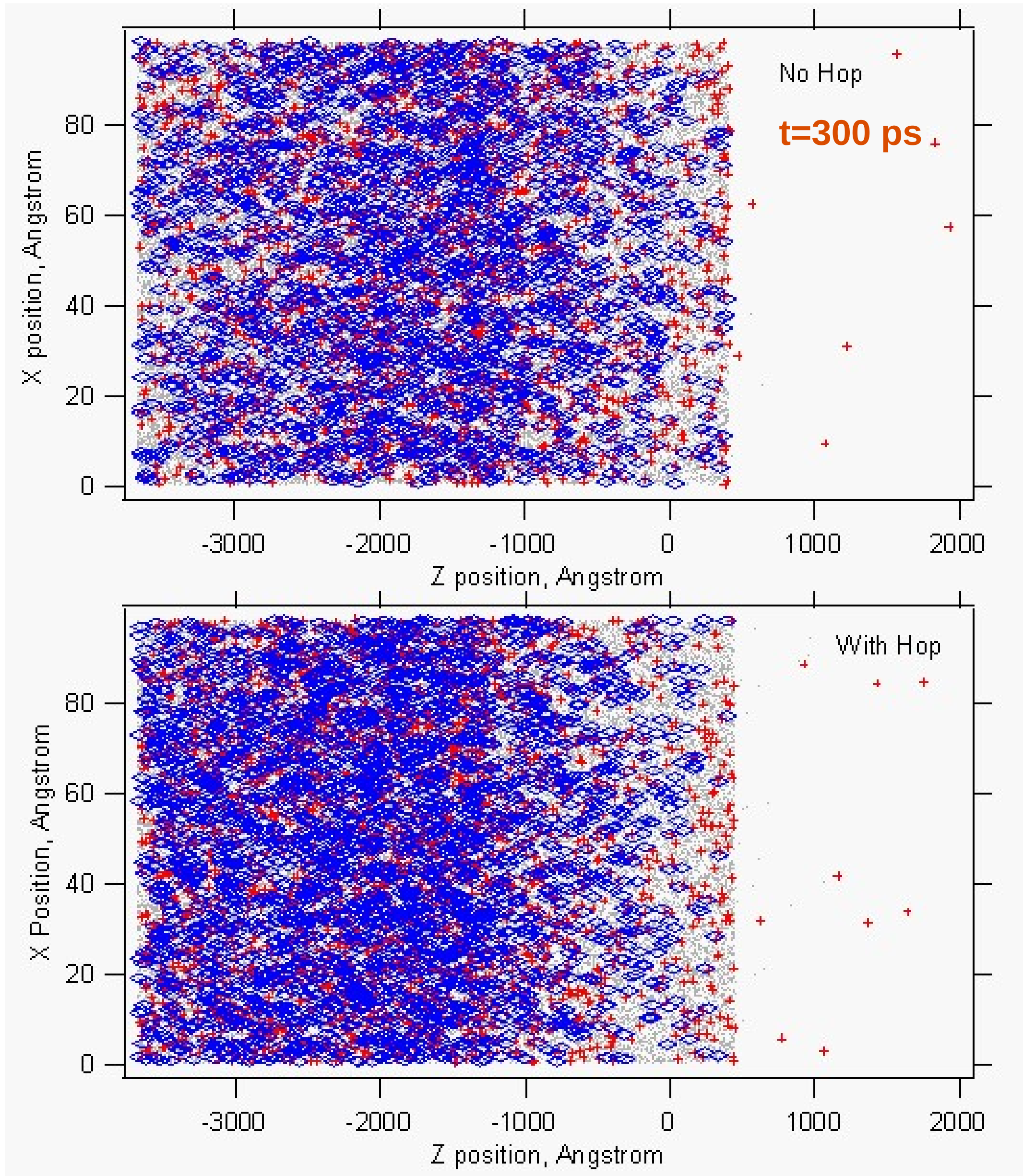
MALDI Ionizationby MD



Ionization vs. Clusters



Ionization with Exciton Hopping



MALDI /MD 1st Results

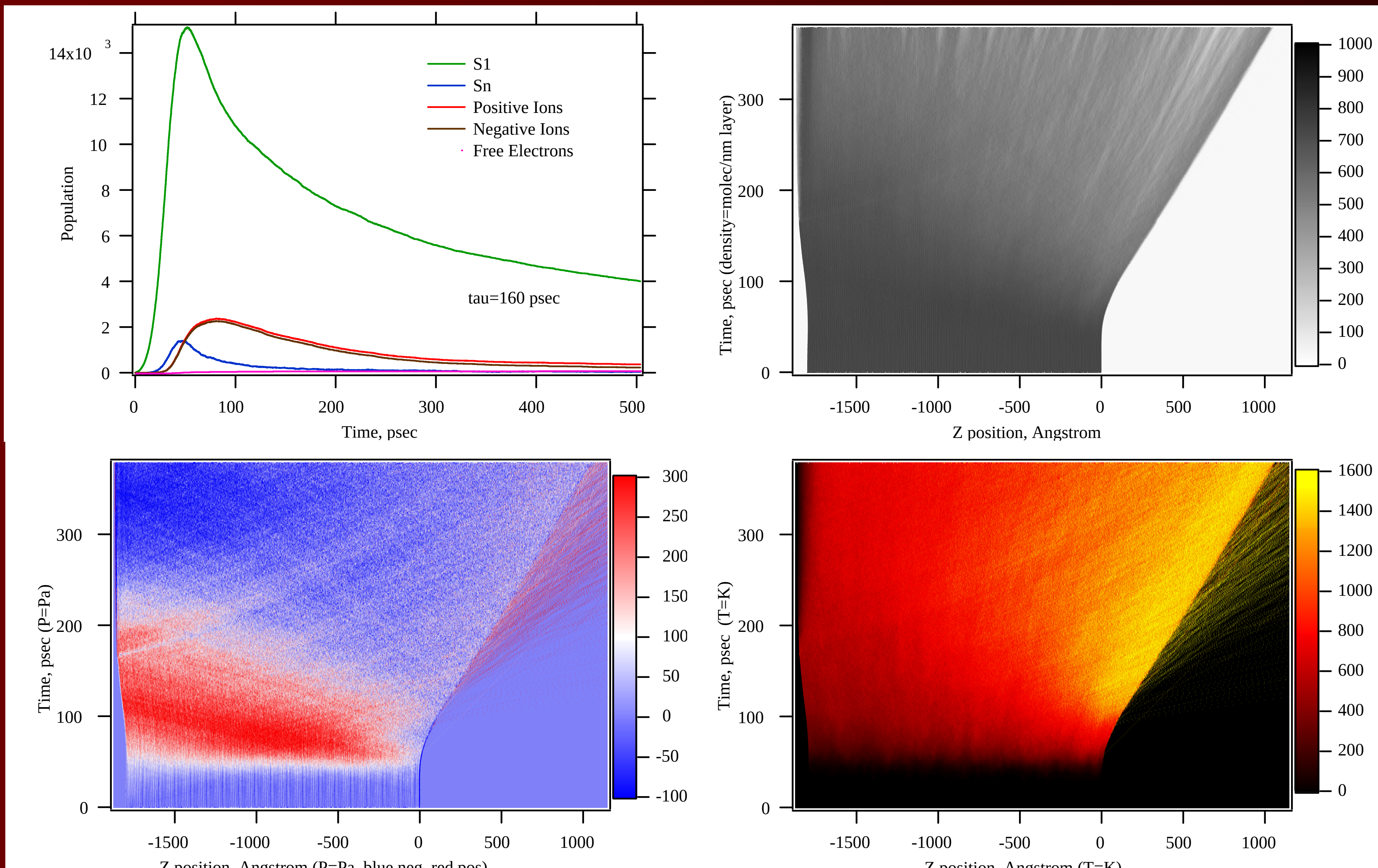
Desorption:

- Longer energy storage vs. non-MALDI
- Both evaporation and ablation

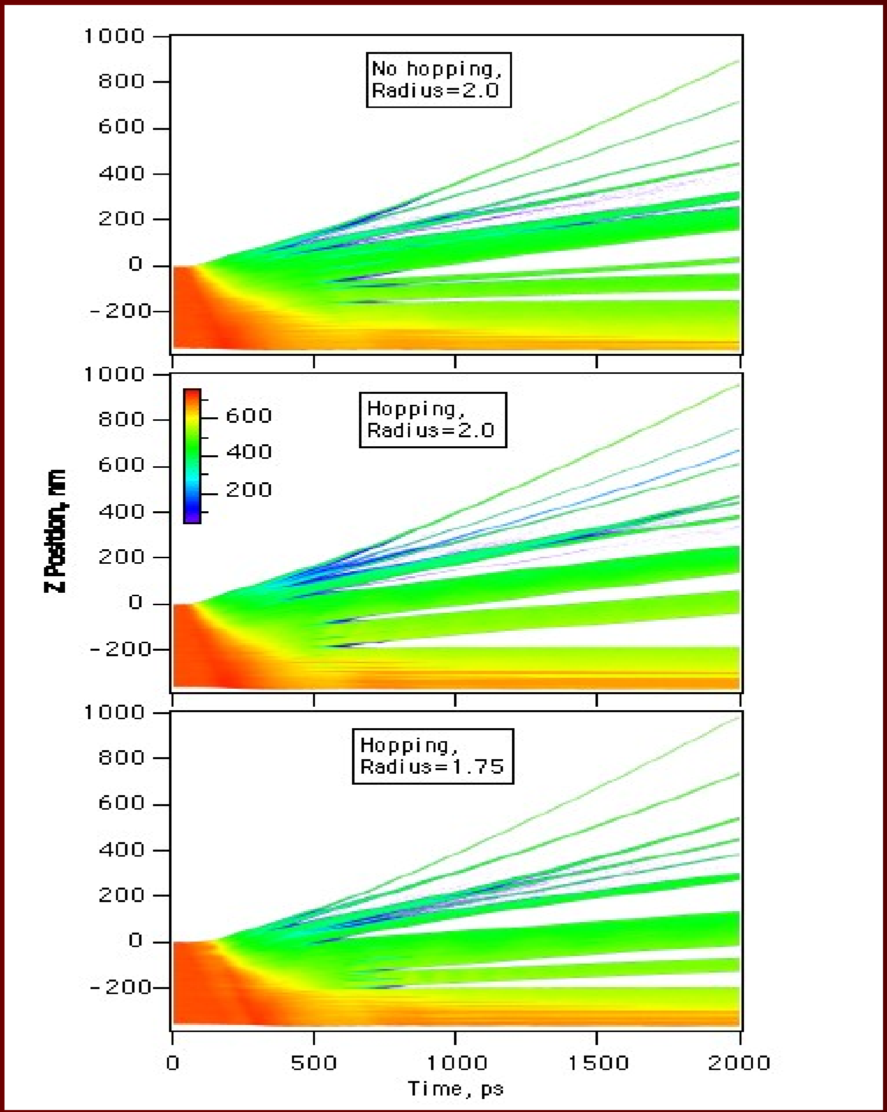
Ionization:

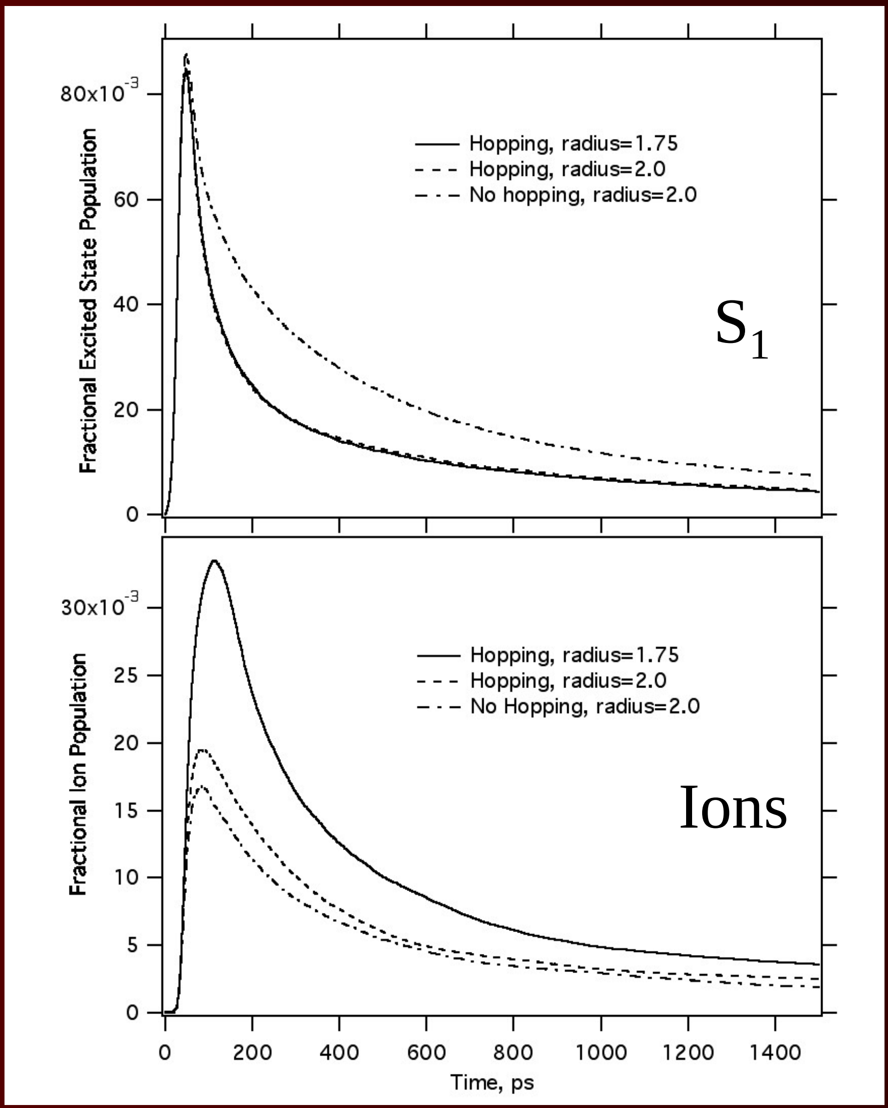
- Ions "evaporate" early
- Hopping enhances ion production
- Coulomb ejection from top layer
- Time progress of populations very similar to continuum model

MALDI Ionizationby MD

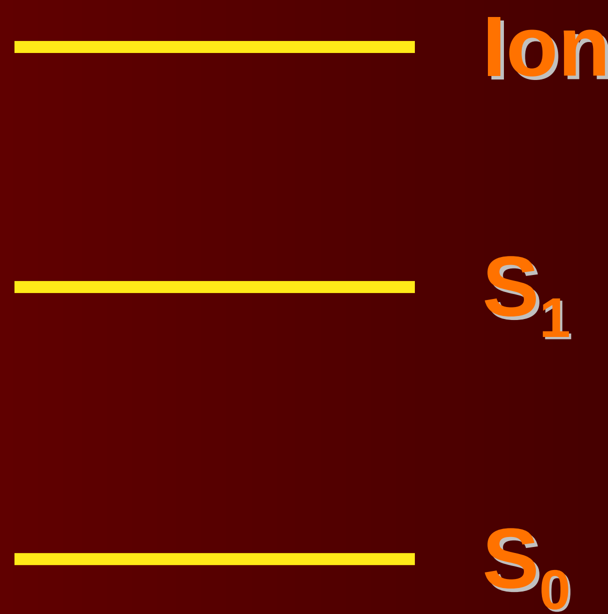


MALDI Ionizationby MD



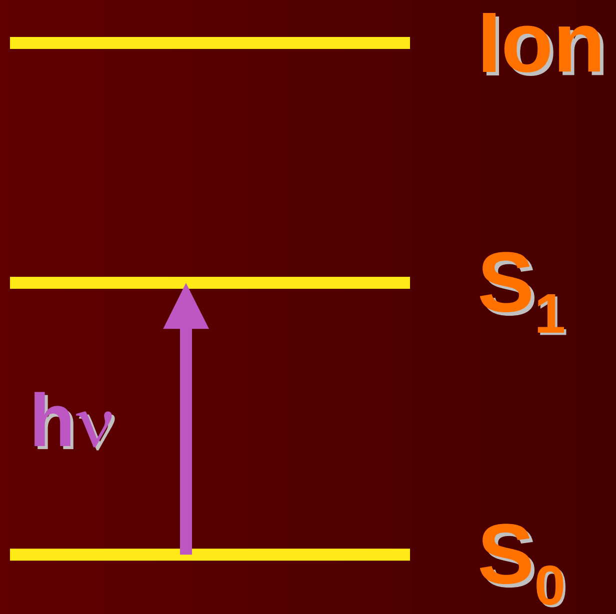


Resonant 2-photon Ionization



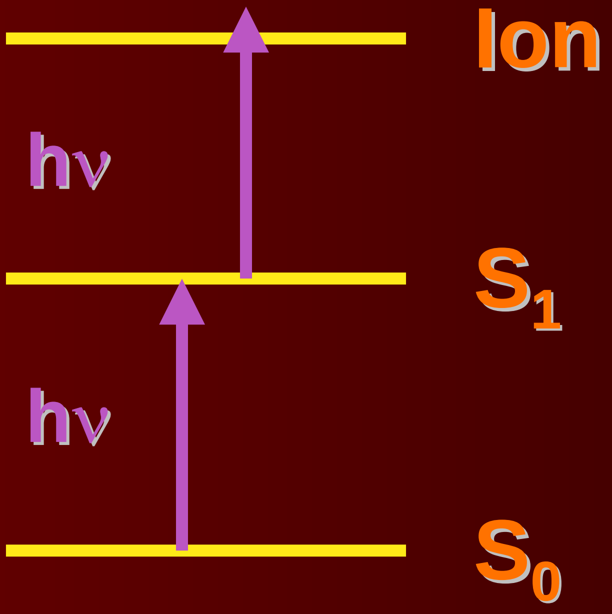
Single matrix molecule

Resonant 2-photon Ionization



Single matrix molecule

Resonant 2-photon Ionization



Single matrix molecule

Possible UV Primary Mechanisms

Exciton Pooling: 2-center

Two-Photon Ionization: 1-center

Excited state proton transfer

Preformed ions

. . . .

Possible UV Primary Mechanisms

Exciton Pooling: 2-center

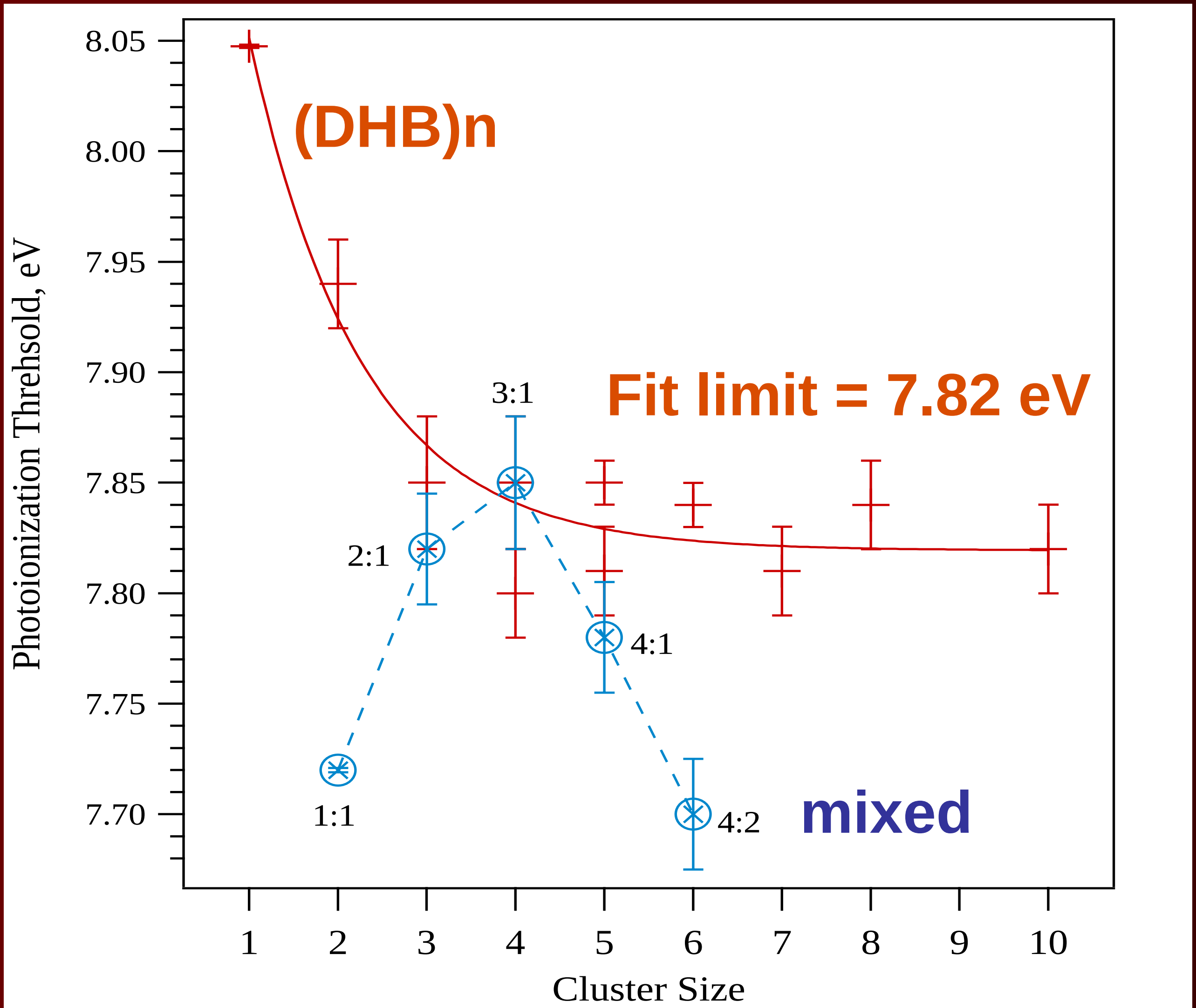
Two-Photon Ionization: 1-center

Excited state proton transfer

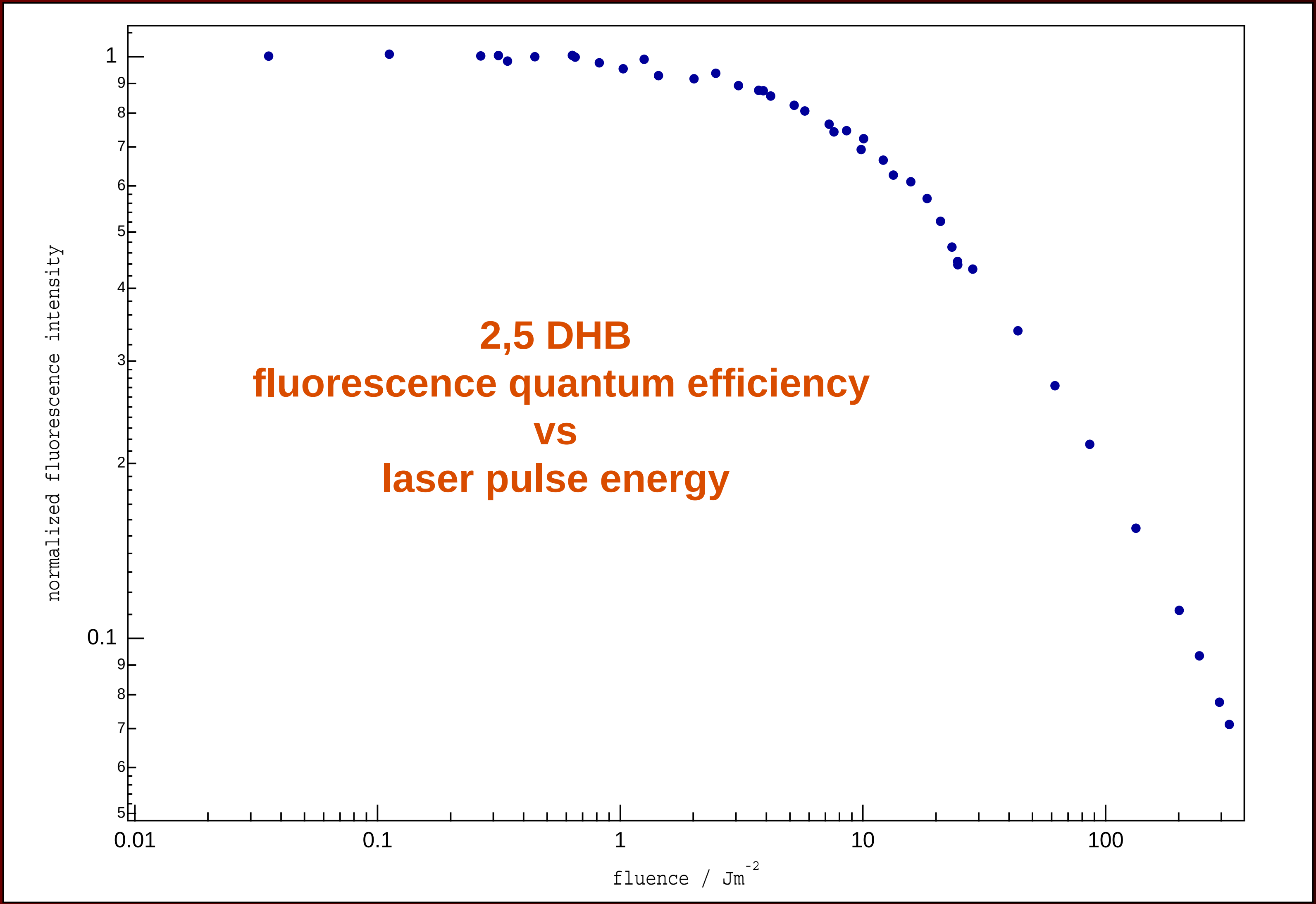
Preformed ions

. . . .

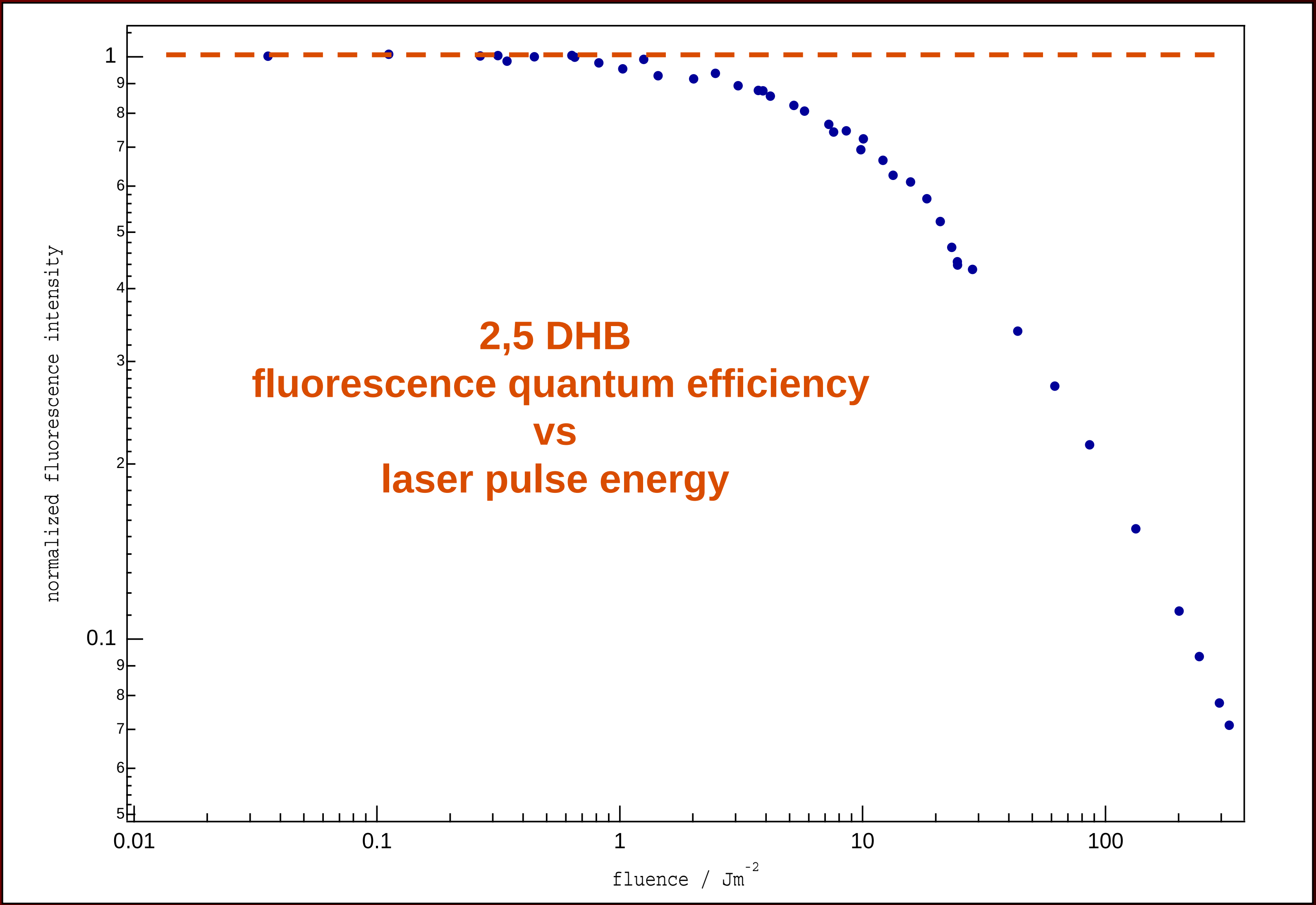
(2,5 DHB)n 1+1` photoionization



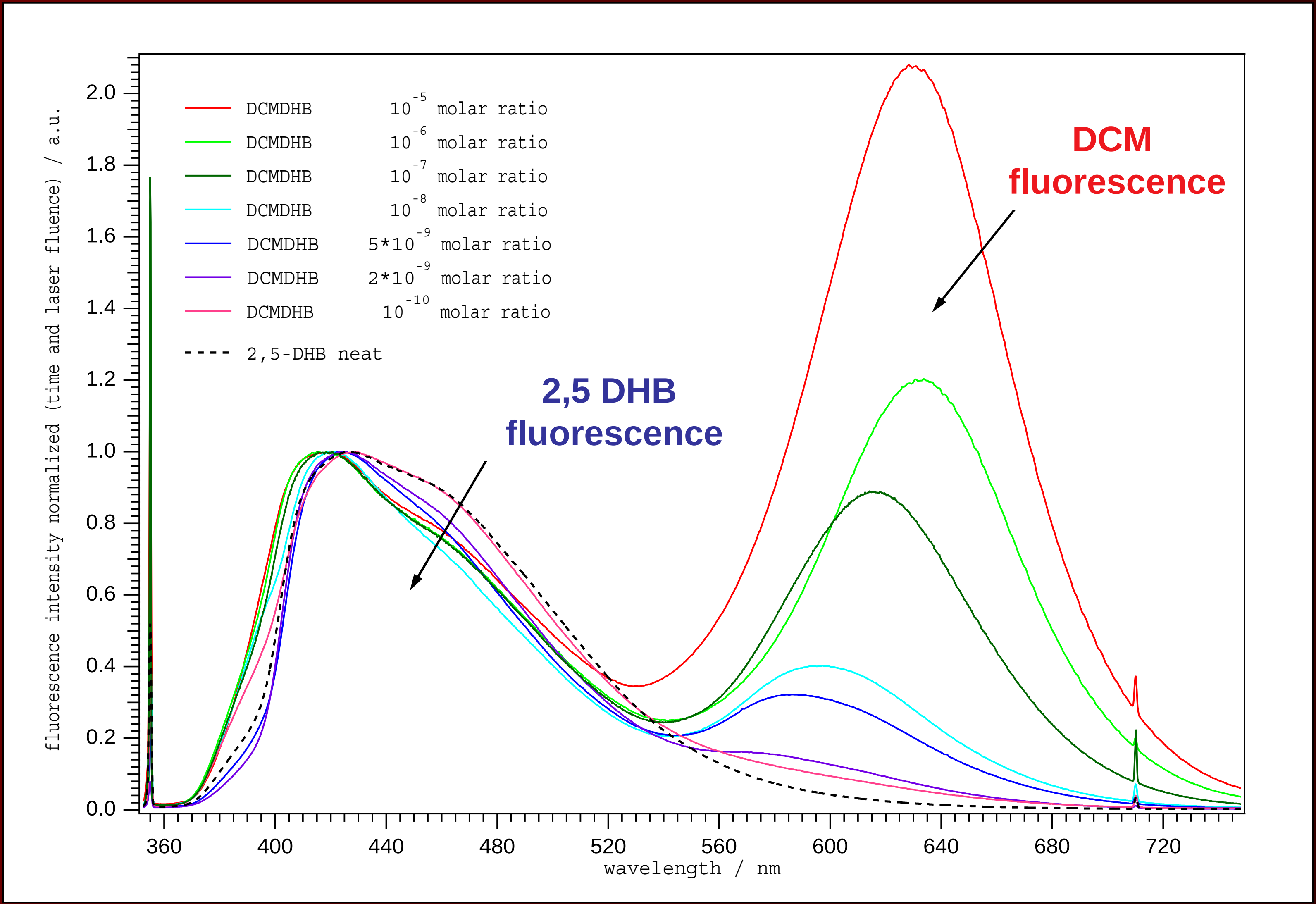
S_1+S_1 Exciton Pooling



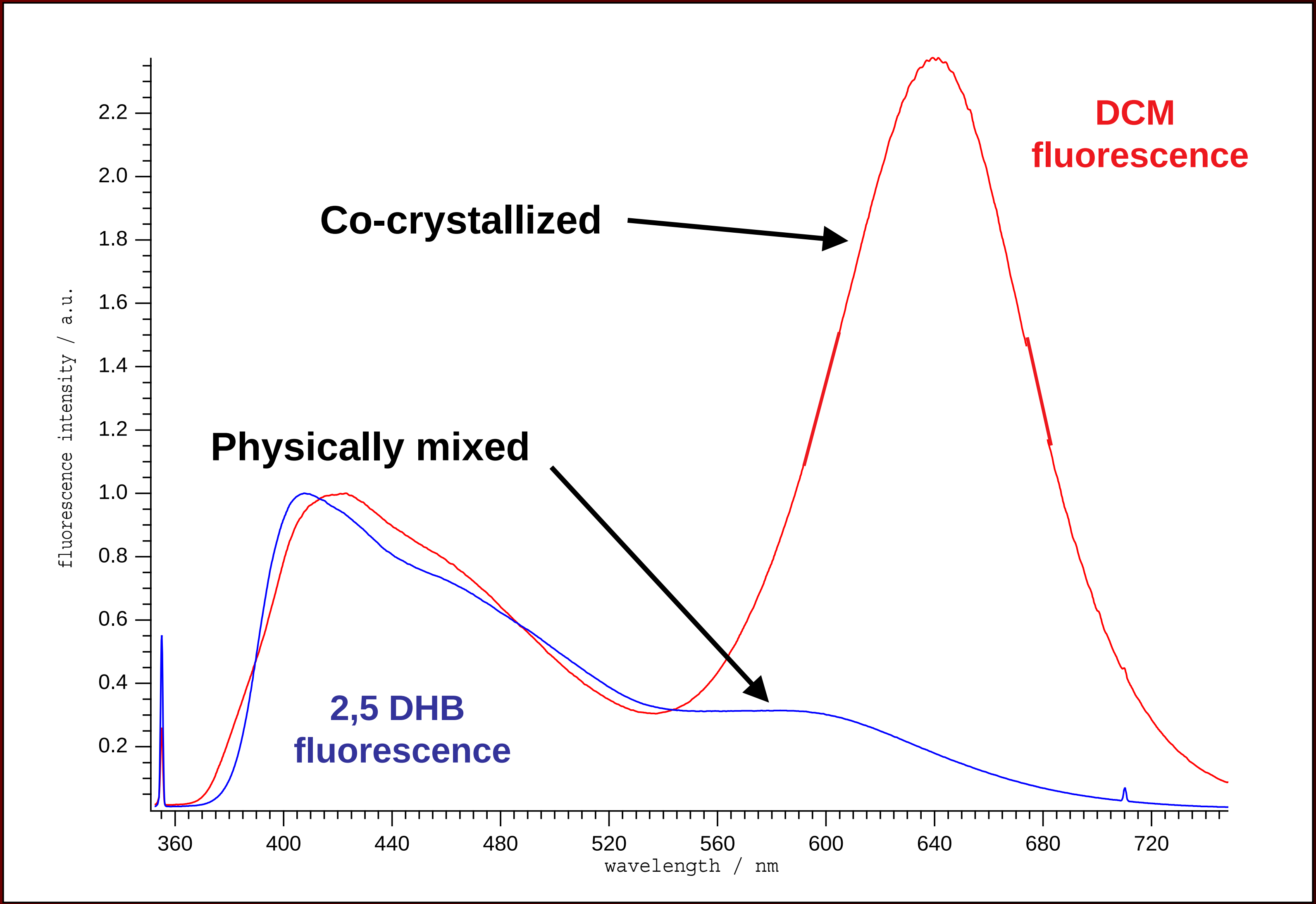
S_1+S_1 Exciton Pooling



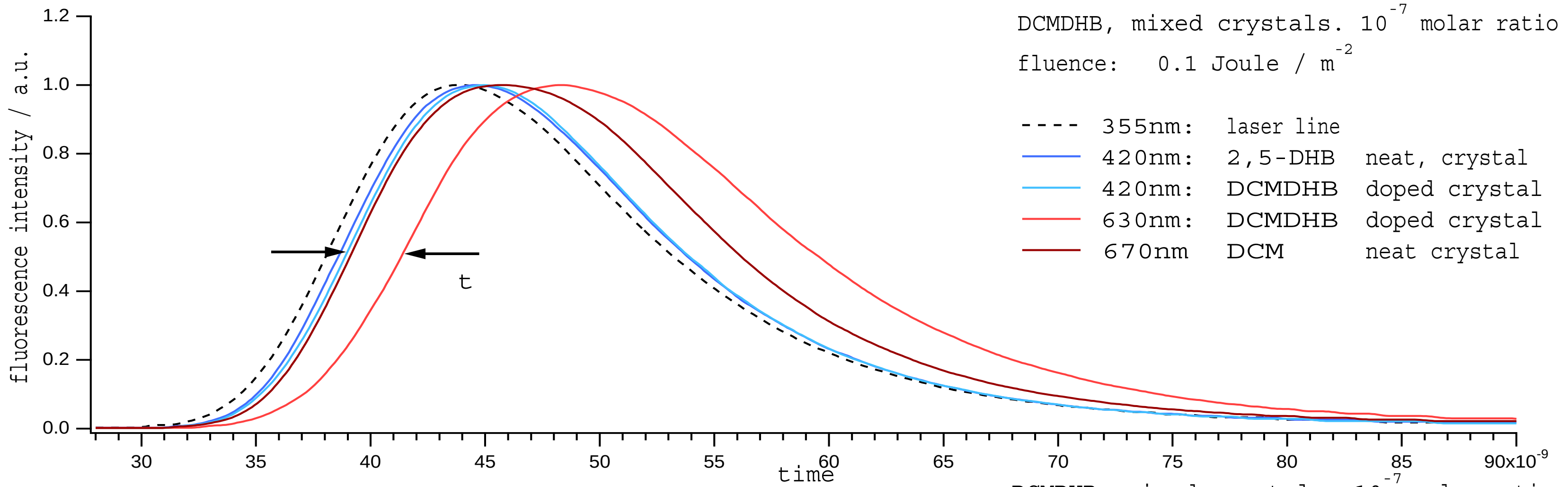
Exciton Migration and Trapping

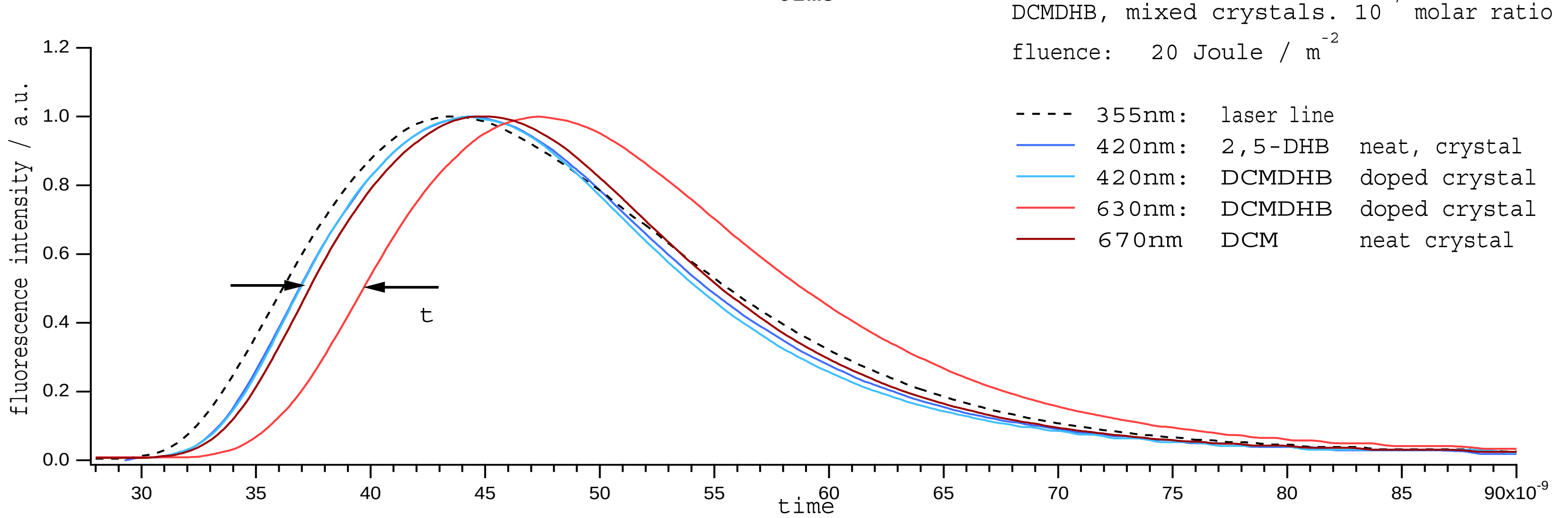


Trapping Control Experiment

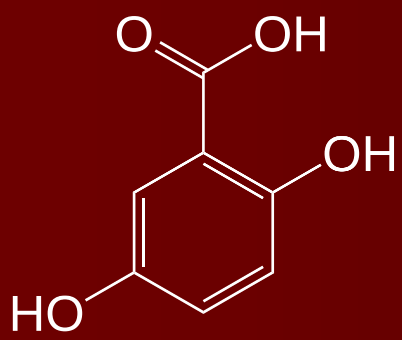


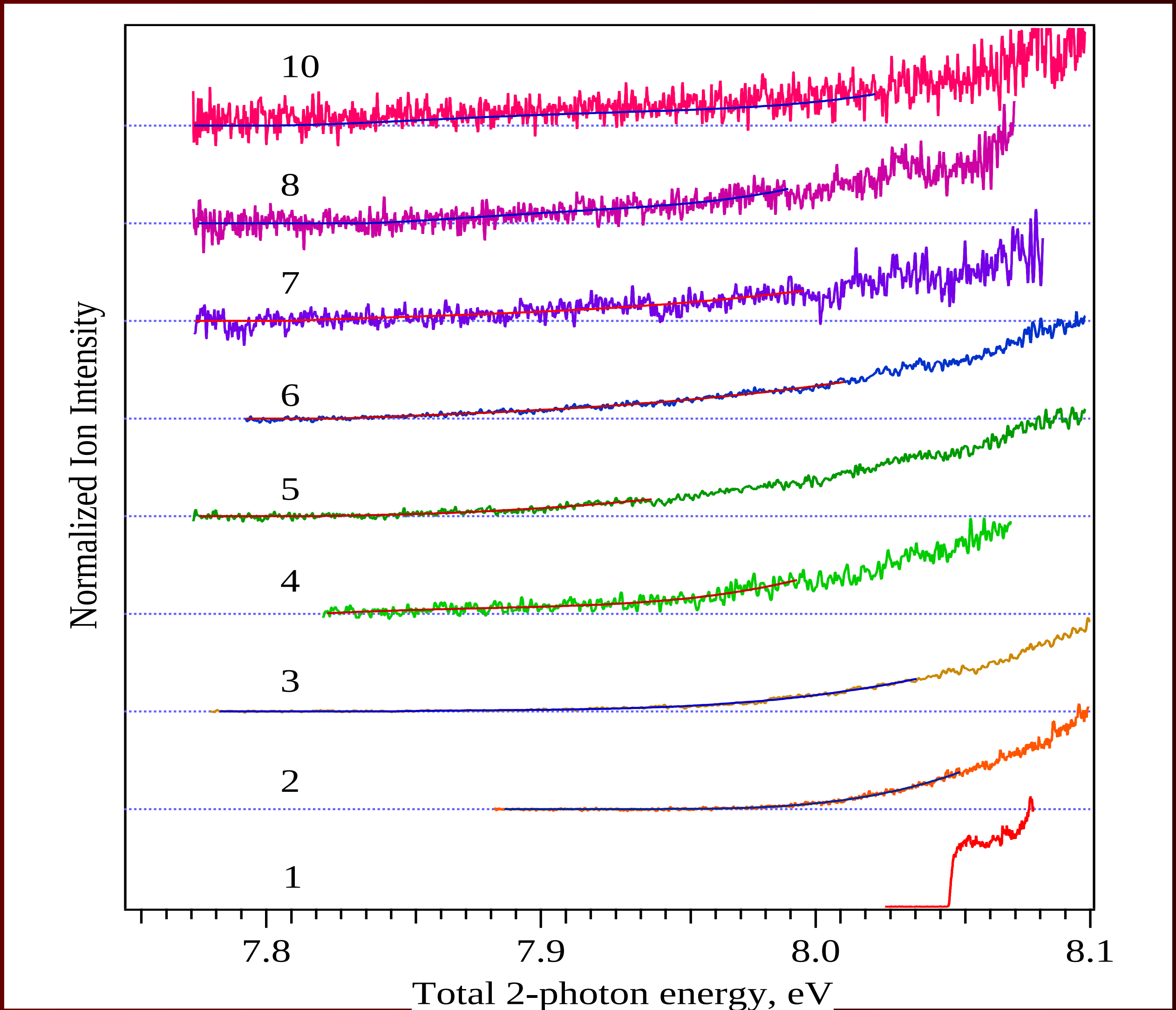
Exciton Diffusion & Pooling: Delayed Trap Fluorescence





(2,5 DHB)n 1+1` photoionization





Matrix-only Differential Eqns.

$$\frac{d[\mathrm{S}_0]}{dt} = -I(t)\sigma_{01}(\lambda)[\mathrm{S}_0] + \frac{[\mathrm{S}_1]}{\tau_1} + I(t)(\sigma_{01}(\lambda)/5)[\mathrm{S}_1] + Dk_{11}[\mathrm{S}_1]^2 + Dk_{1n}[\mathrm{S}_1][\mathrm{S}_n] + k_{I0}[Ions]$$

$$\frac{d[\mathrm{S}_1]}{dt} = I(t)\sigma_{01}(\lambda)[\mathrm{S}_0] - \frac{[\mathrm{S}_1]}{\tau_1} - I(t)(\sigma_{01}(\lambda)/5)[\mathrm{S}_1] - I(t)\sigma_{1n}(\lambda)[\mathrm{S}_1] + k_{n1}[\mathrm{S}_n] - 2Dk_{11}[\mathrm{S}_1]^2 - Dk_{1n}[\mathrm{S}_1][\mathrm{S}_n]$$

$$\frac{d[\mathrm{S}_n]}{dt} = I(t)\sigma_{1n}(\lambda)[\mathrm{S}_1] - k_{n1}[\mathrm{S}_n] - k_{therm}[\mathrm{S}_n] + Dk_{11}[\mathrm{S}_1]^2 - Dk_{1n}[\mathrm{S}_1][\mathrm{S}_n]$$

$$\frac{d[\mathrm{Ions}]}{dt} = k_{therm}[\mathrm{S}_n] + Dk_{1n}[\mathrm{S}_1][\mathrm{S}_n] - Dk_{I0}[\mathrm{Ions}]$$

$$\frac{dE}{dt} = I(t)\sigma_{01}(\lambda)[\mathrm{S}_0](h\upsilon - E(S_1)) + \frac{1}{\tau_1}\left([\mathrm{S}_1]E(S_1)(1-\Phi(S_1)) + k_{n1}[\mathrm{S}_n](E(S_n)-E(S_1))\right)$$
$$+Dk_{1n}[\mathrm{S}_1][\mathrm{S}_n](E(S_1)+E(S_n)-IP) + Dk_{I0}[Ions]IP$$

$$Temperature = E/(kf)$$

$$k_{therm} = 9X10^{15}e^{(E(S_1)-IP)/kT}$$

The Plume Expansion

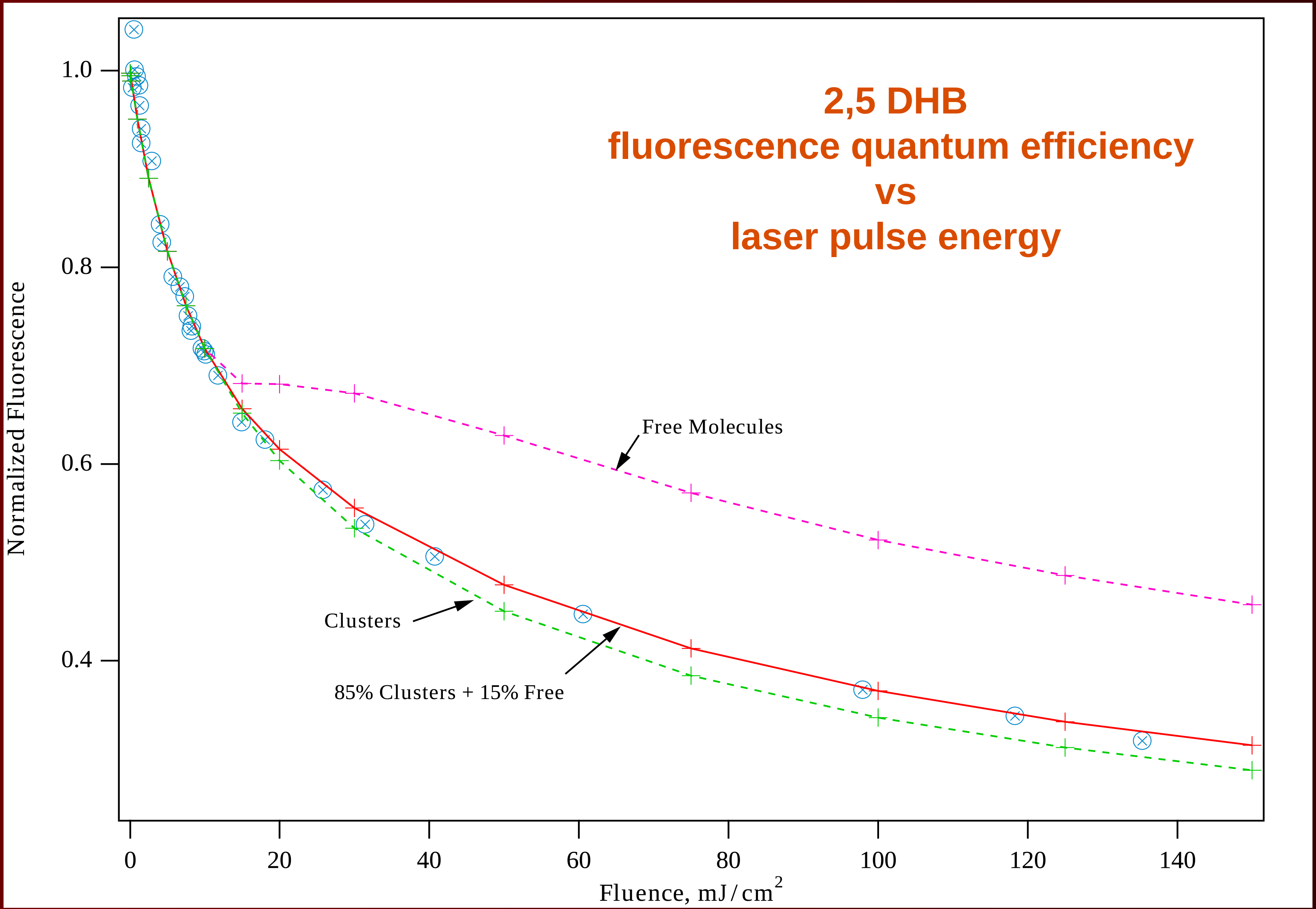
When $T=T_{sublimation}$, start expansion

During expansion, scale rates by P/P_0:

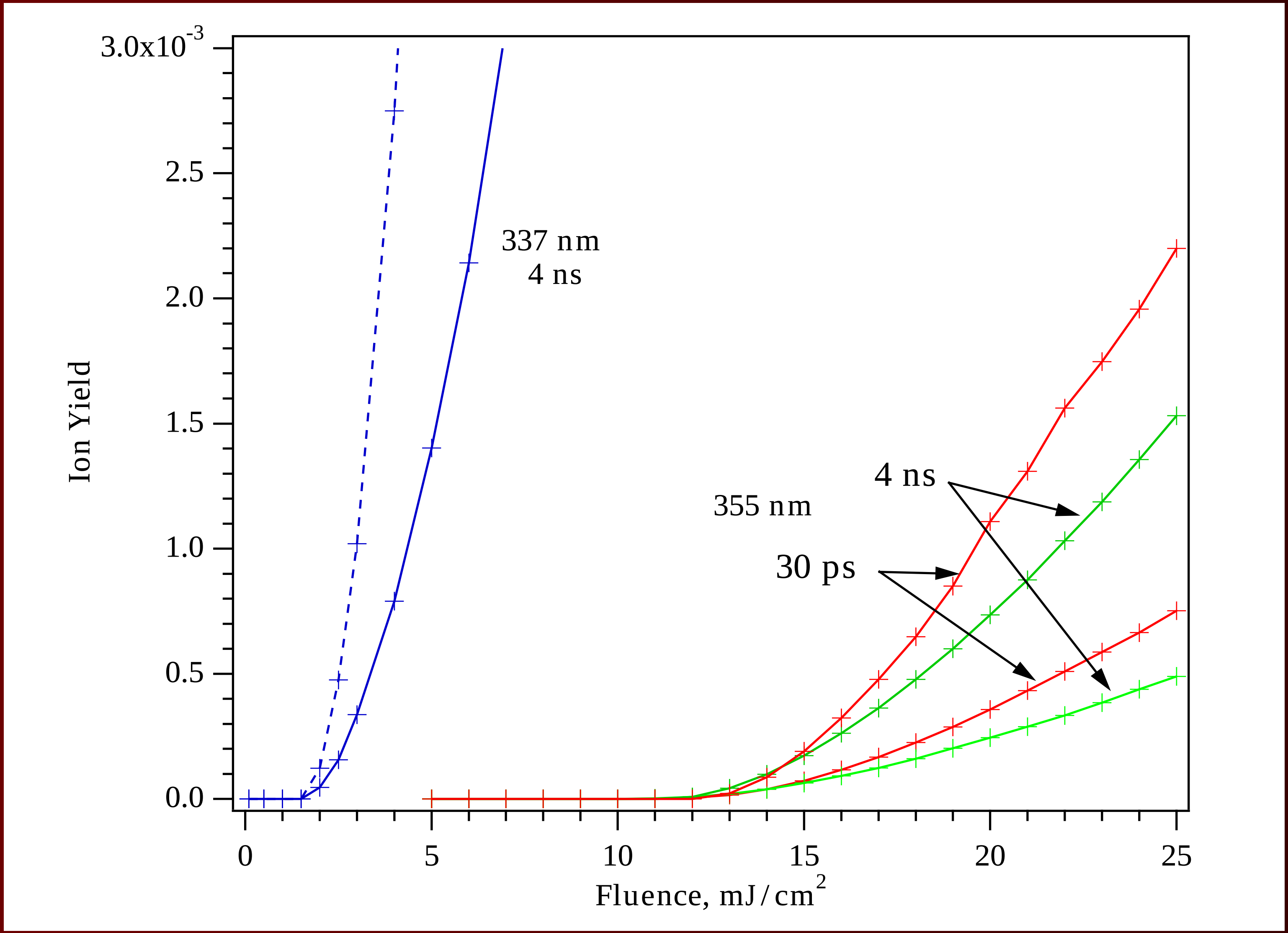
- pooling ↓
- S_1 lifetime ↑
- recombination ↓

Correct for large cluster fraction (85%)

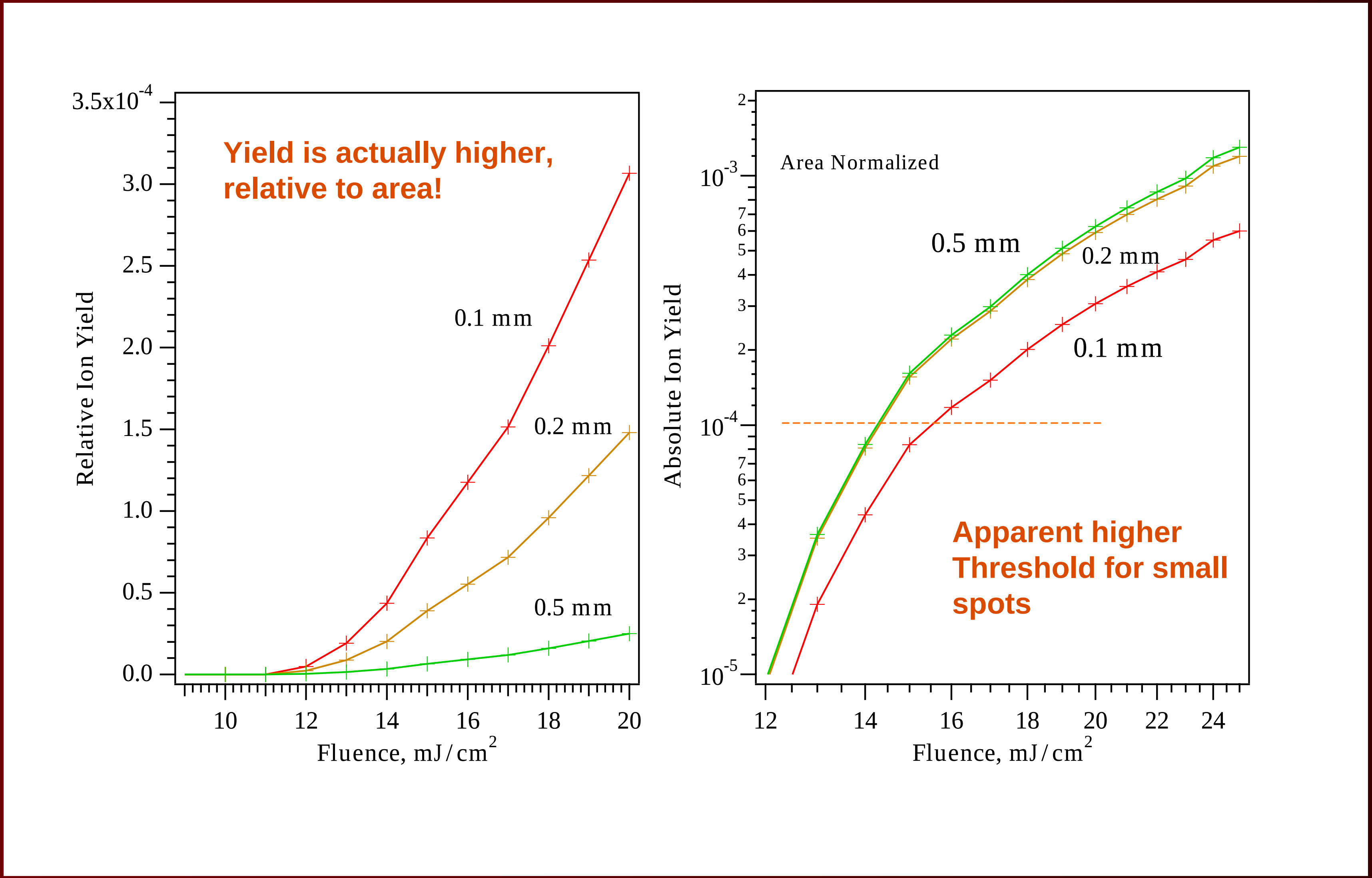
Fluorescence Quenching



Wavelength, Fluence, and Pulse Length Effects



Spot Size Effects



Secondary In-Plume Reactions: Proton Transfer

Matrix – analyte reactions:

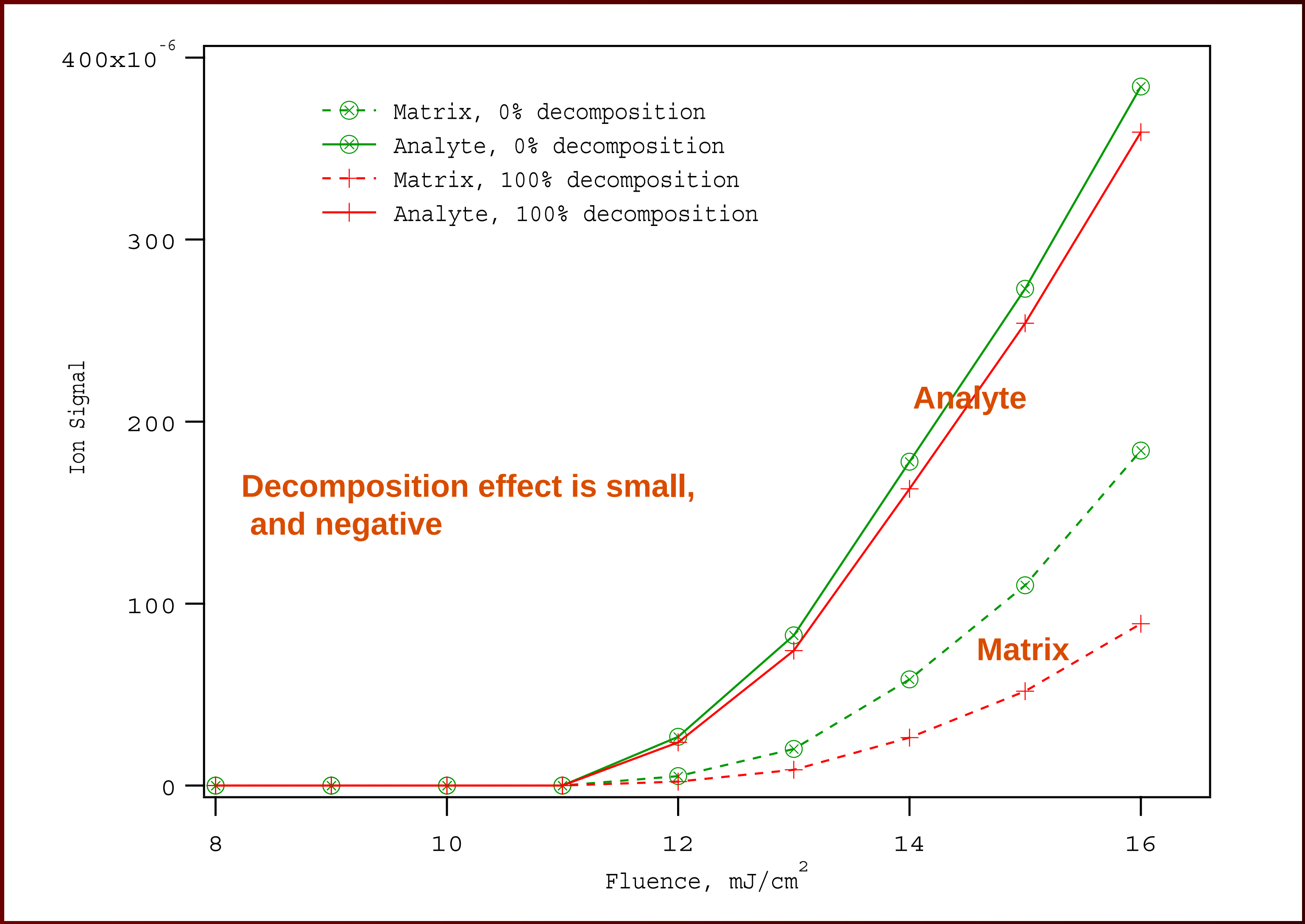
$$MH^+ + A \rightarrow M + AH^+$$

Analyte – analyte reactions:

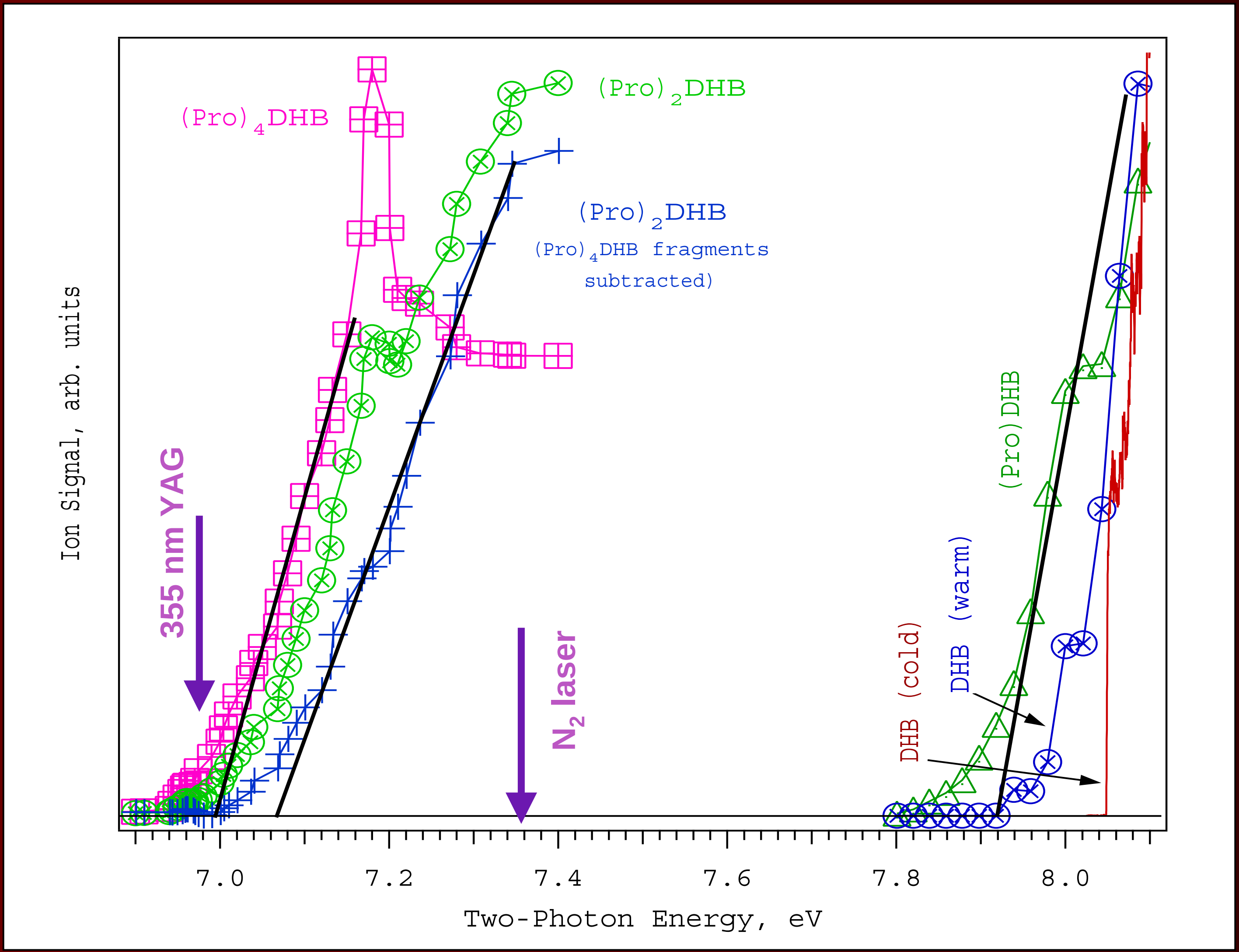
$$AH^+ + B \rightarrow A + BH^+$$

The relevant parameter is the gas-phase proton affinity

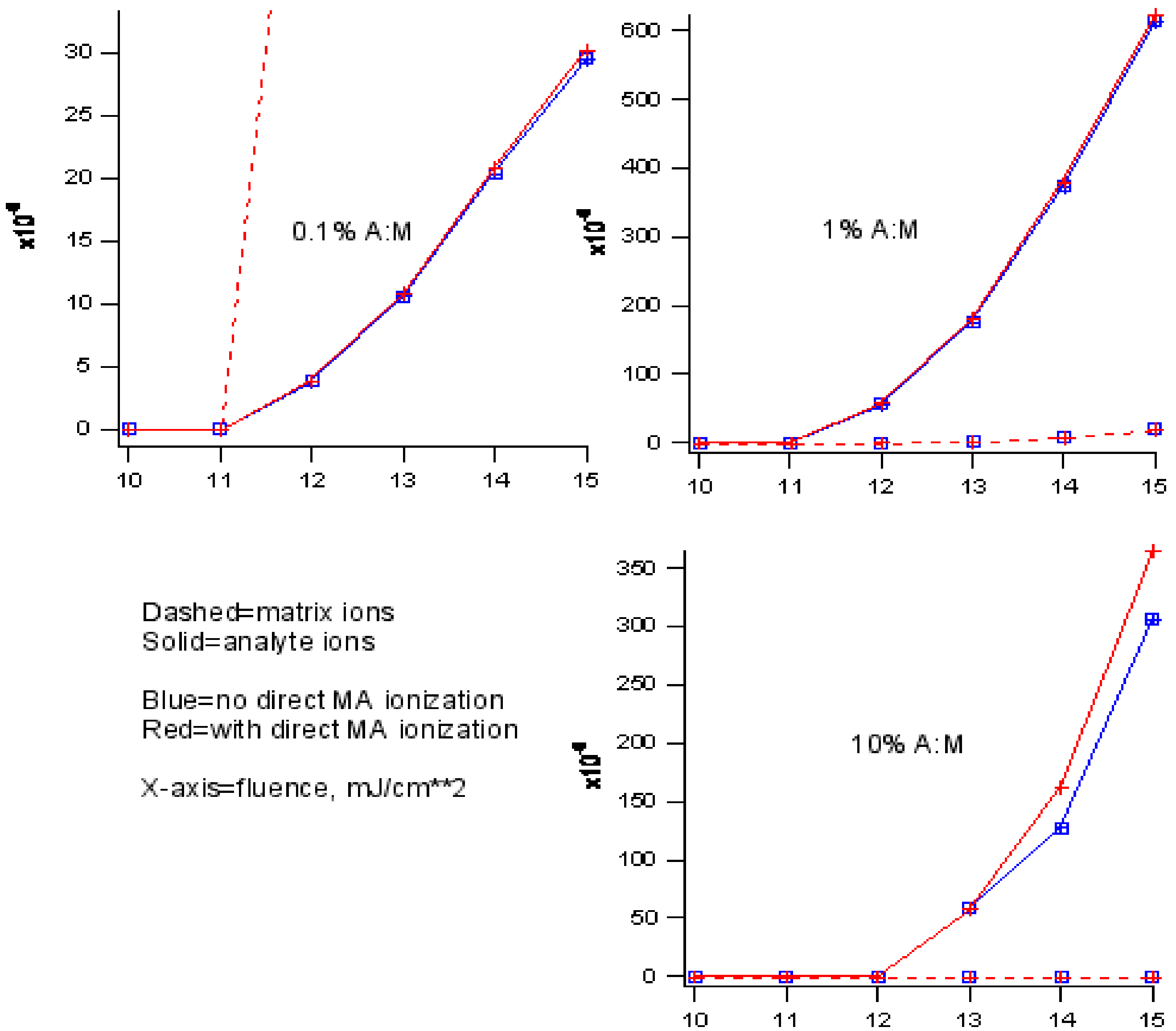
Matrix Decomposition



2,5 DHB-proline clusters



Cluster R2PI

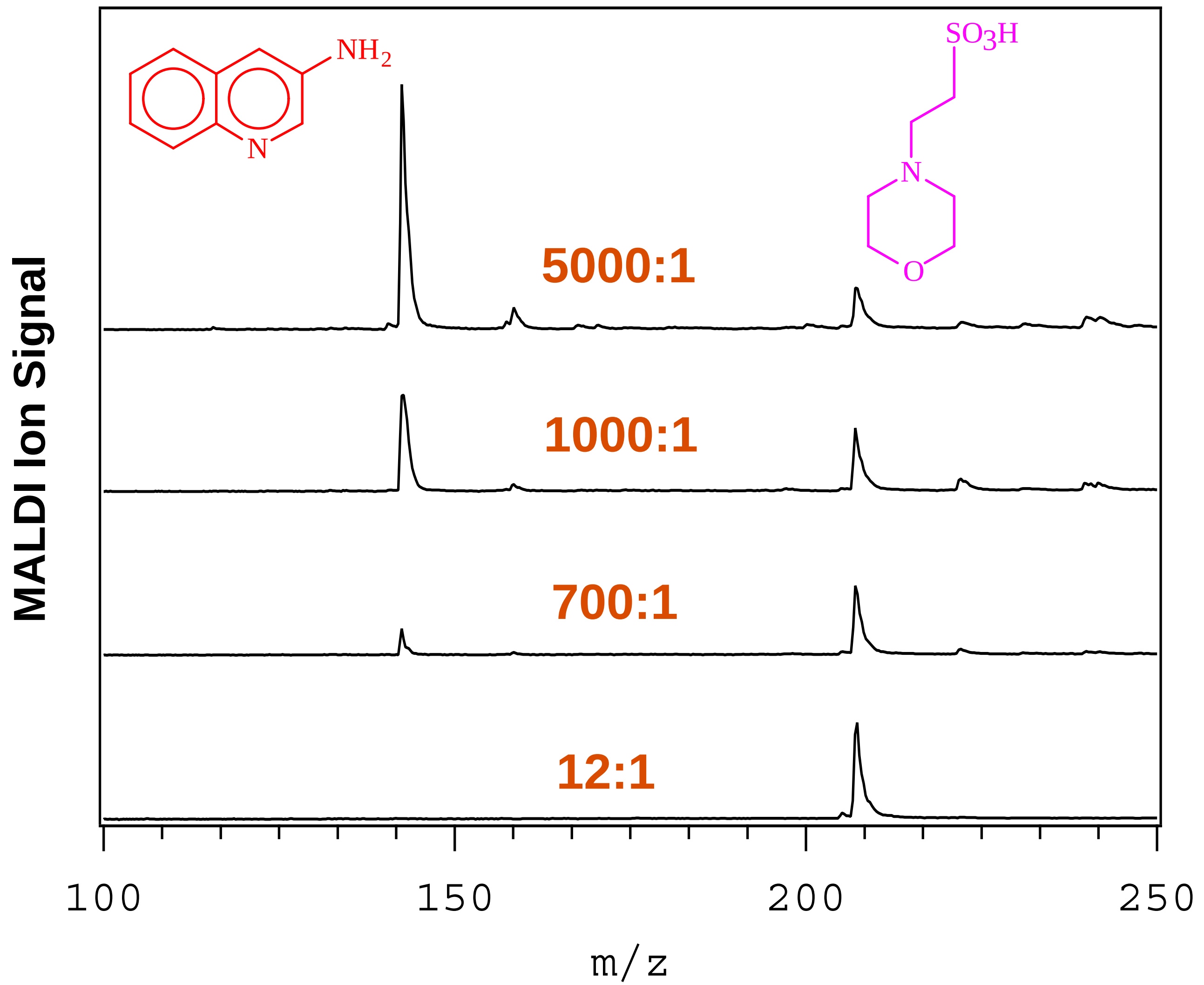


Dashed=matrix ions
Solid=analyte ions

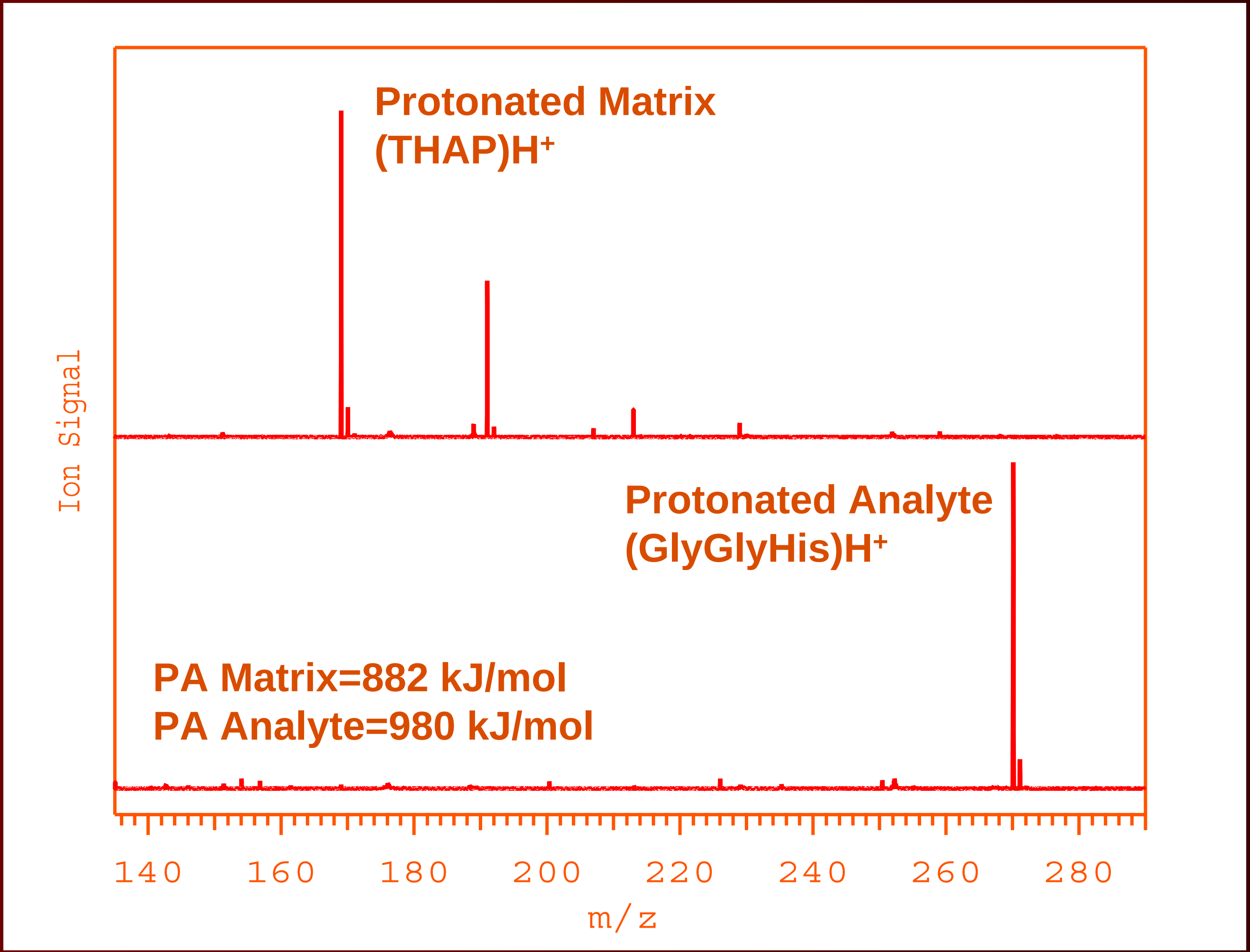
Blue=no direct MA ionization
Red=with direct MA ionization

X-axis=fluence, mJ/cm**2

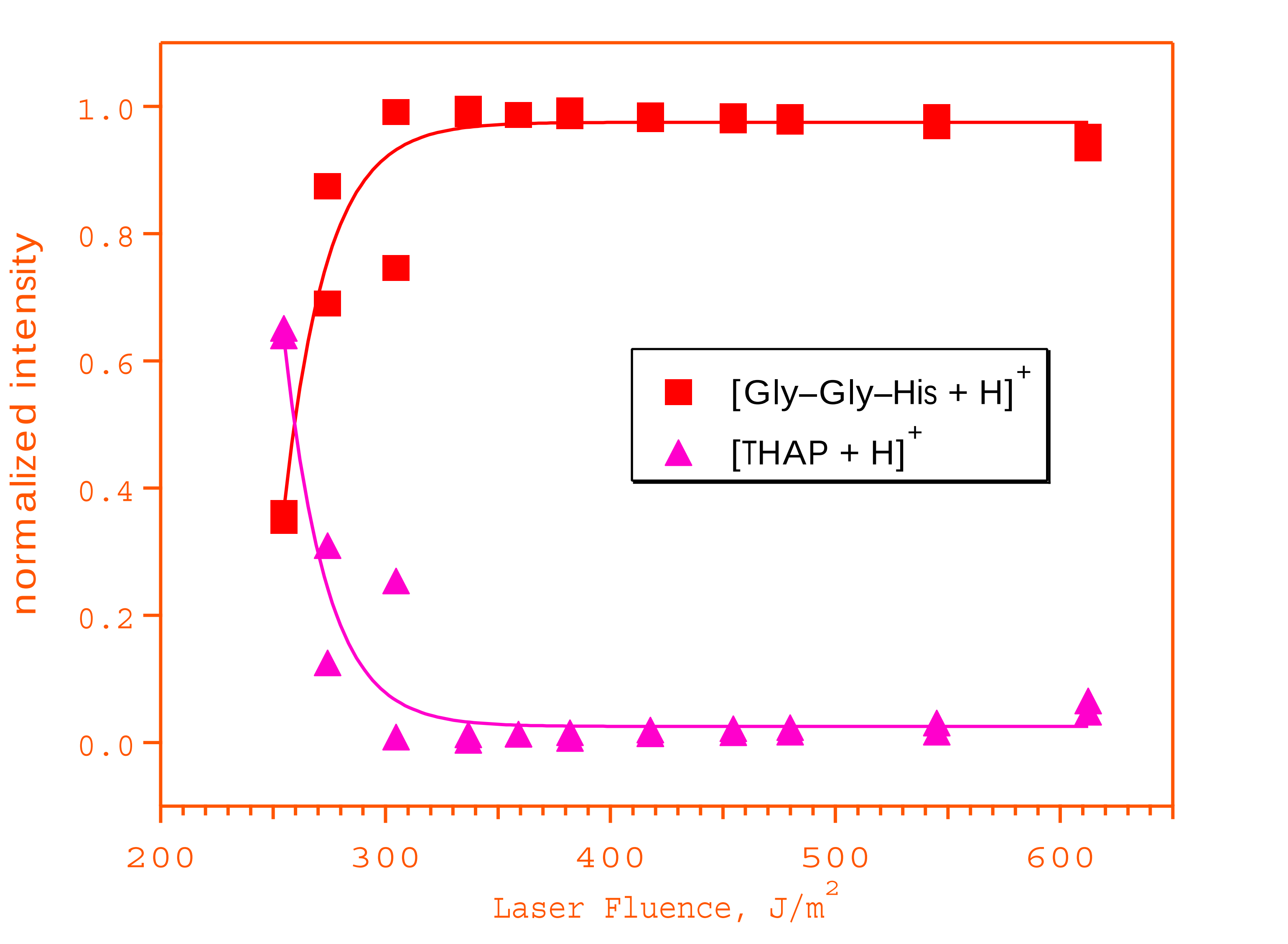
Matrix Suppression Effect



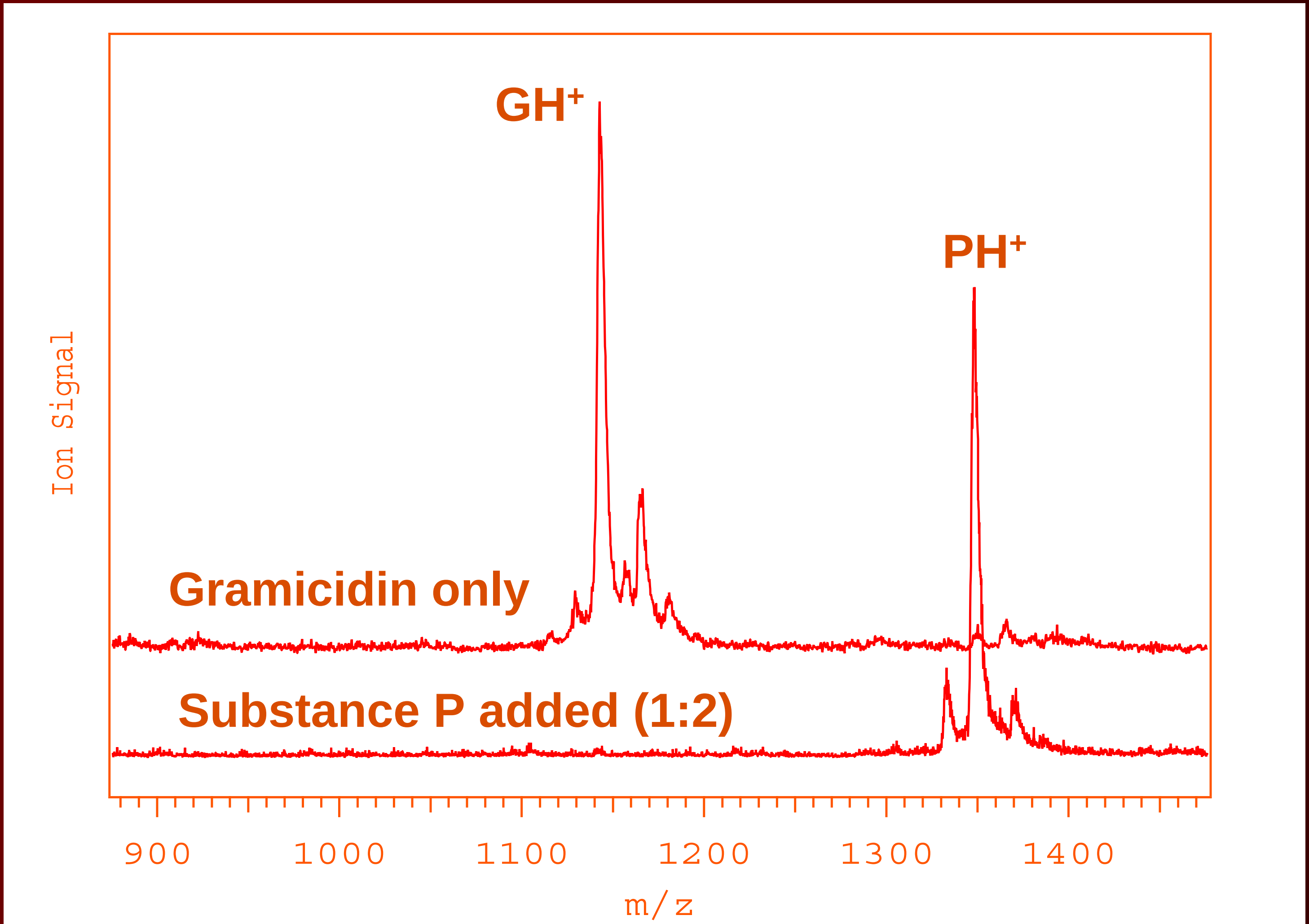
Proton Transfer Matrix Suppression



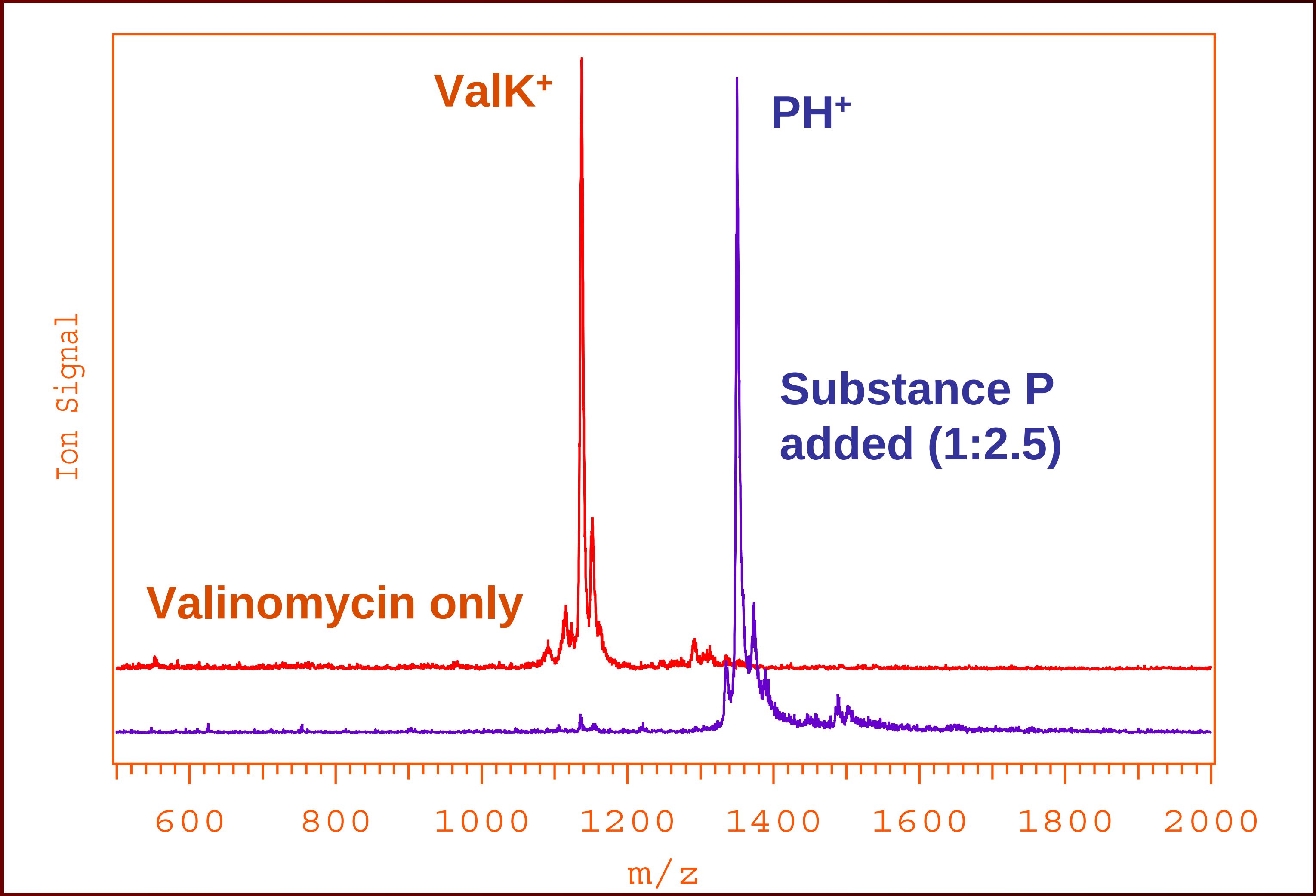
Matrix Suppression and Plume Density



Analyte Suppression Effect: Similar Ions



Analyte Suppression Effect: Dissimilar Ions



Adding Analyte to the Continuum Model

$M^+ + A \Leftrightarrow M + A^+$

$$\frac{d[\mathrm{A}]}{dt} = -k_{MA}\left[\mathrm{M}^+\right][\mathrm{A}] + k_{AM}[M]\left[\mathrm{A}^+\right]$$

$$\frac{d\left[\mathrm{A}^+\right]}{dt} = k_{MA}\left[\mathrm{M}^+\right][\mathrm{A}] - k_{AM}[M]\left[\mathrm{A}^+\right]$$

Arrhenius Rates:

$$k_{MA} = Ae^{-EA/kT} \qquad k_{AM} = Ae^{-(EA+\Delta G)/kT}$$

$$A = \pi(D_M + D_A)^2 F(1-F)n\sqrt{{V_M}^2 + {V_A}^2}$$

Activation Energy:

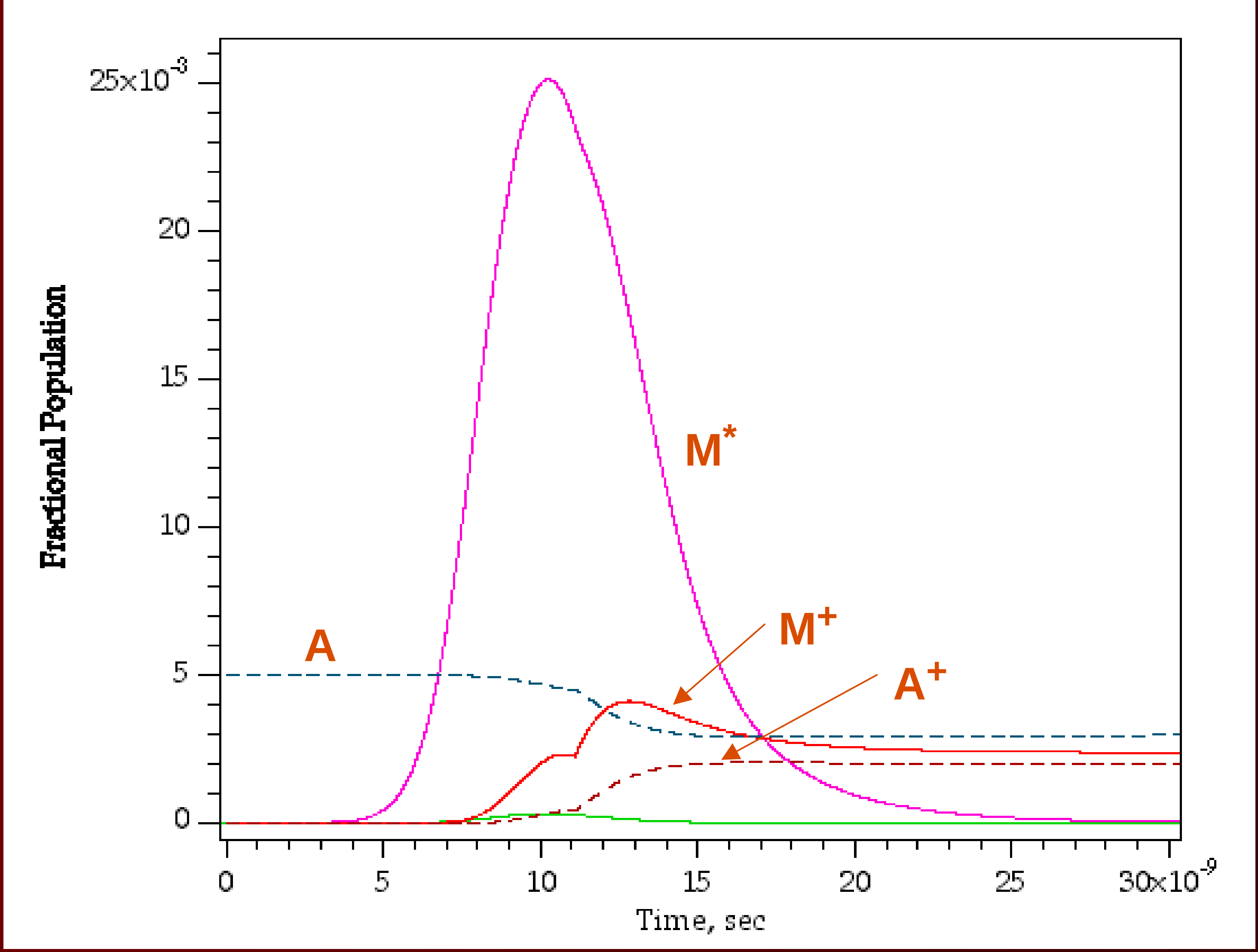
$$EA = \Delta G - \lambda \ln\left(\frac{1}{1+e^{-\Delta G/\lambda}}\right)$$

Volume Correction:

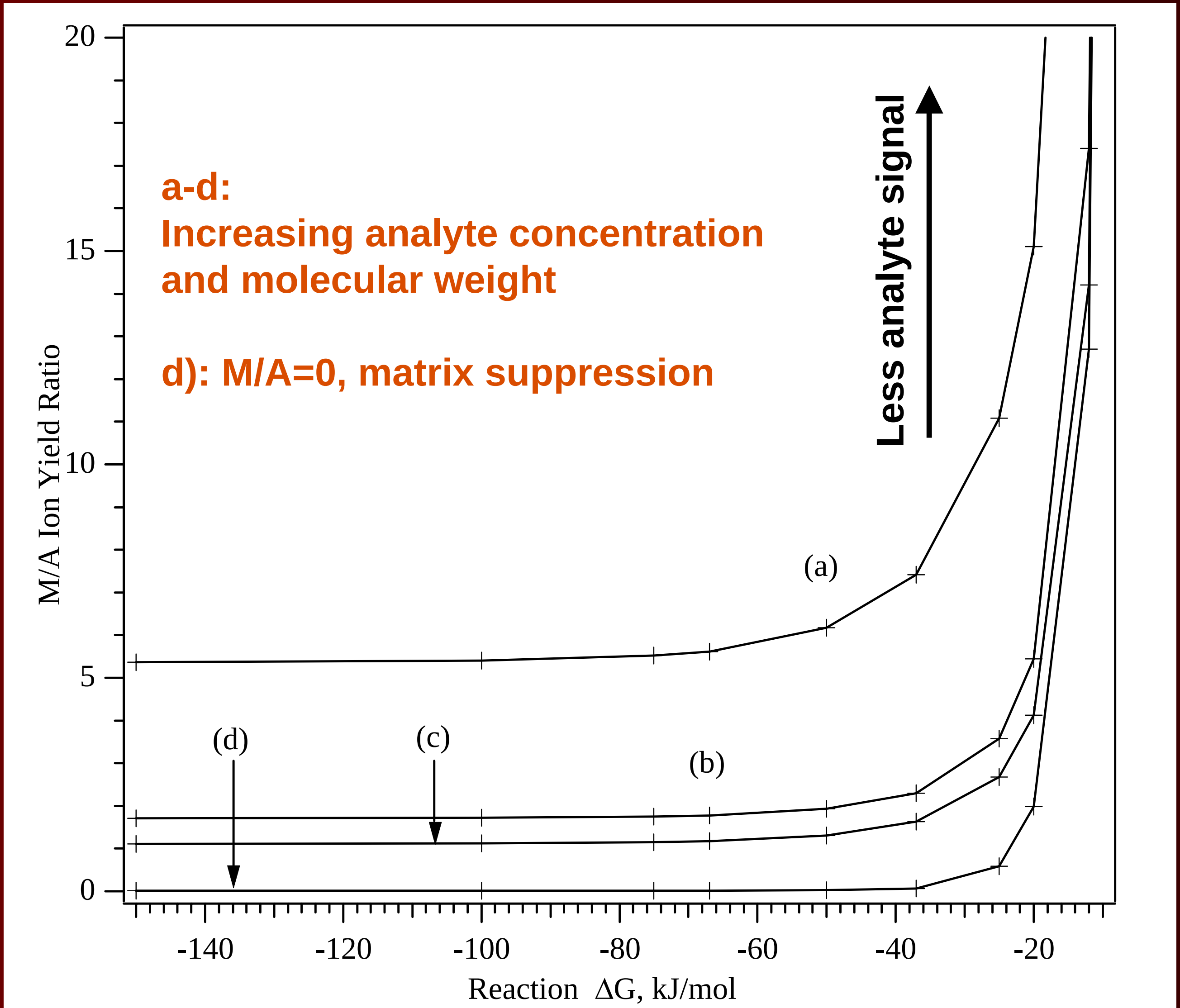
$$\left|1 + \left[\left(\frac{D_A}{D_M}\right)^2 - 1\right]\frac{P}{P_0}\right|$$

No adjustable parameters

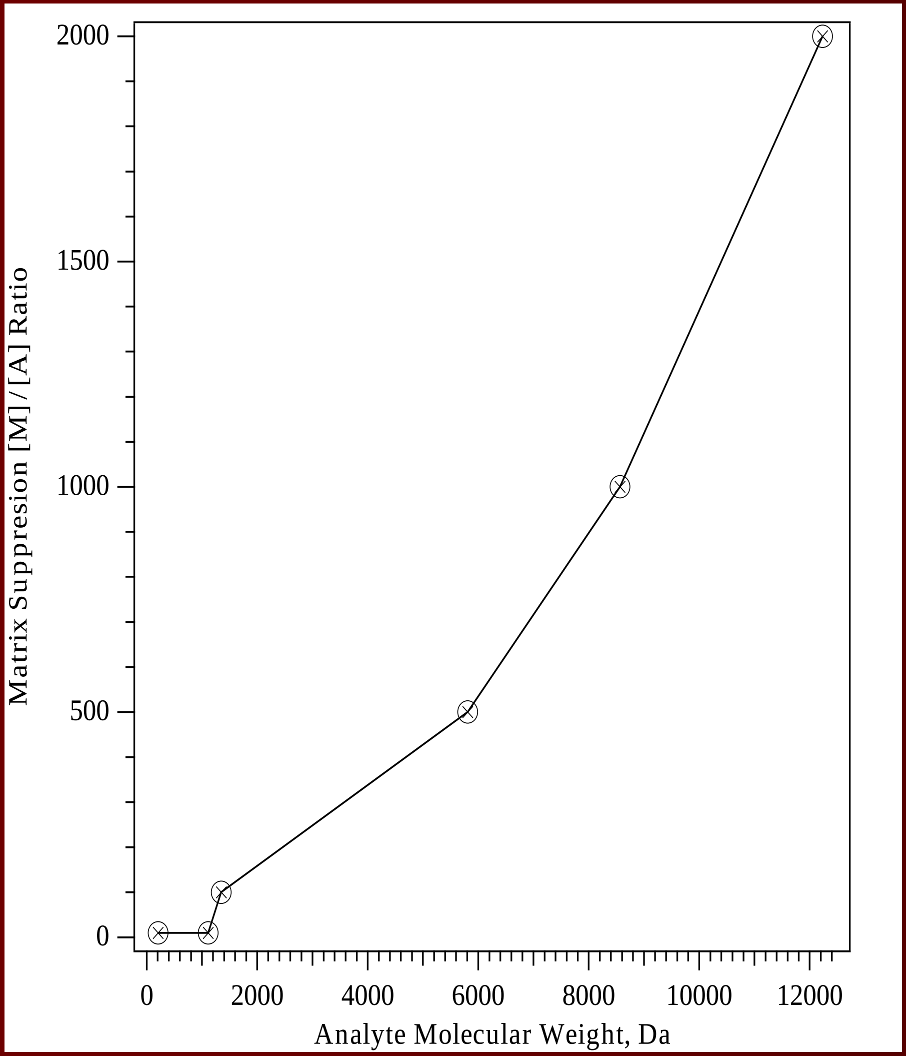
Example Results with Analyte

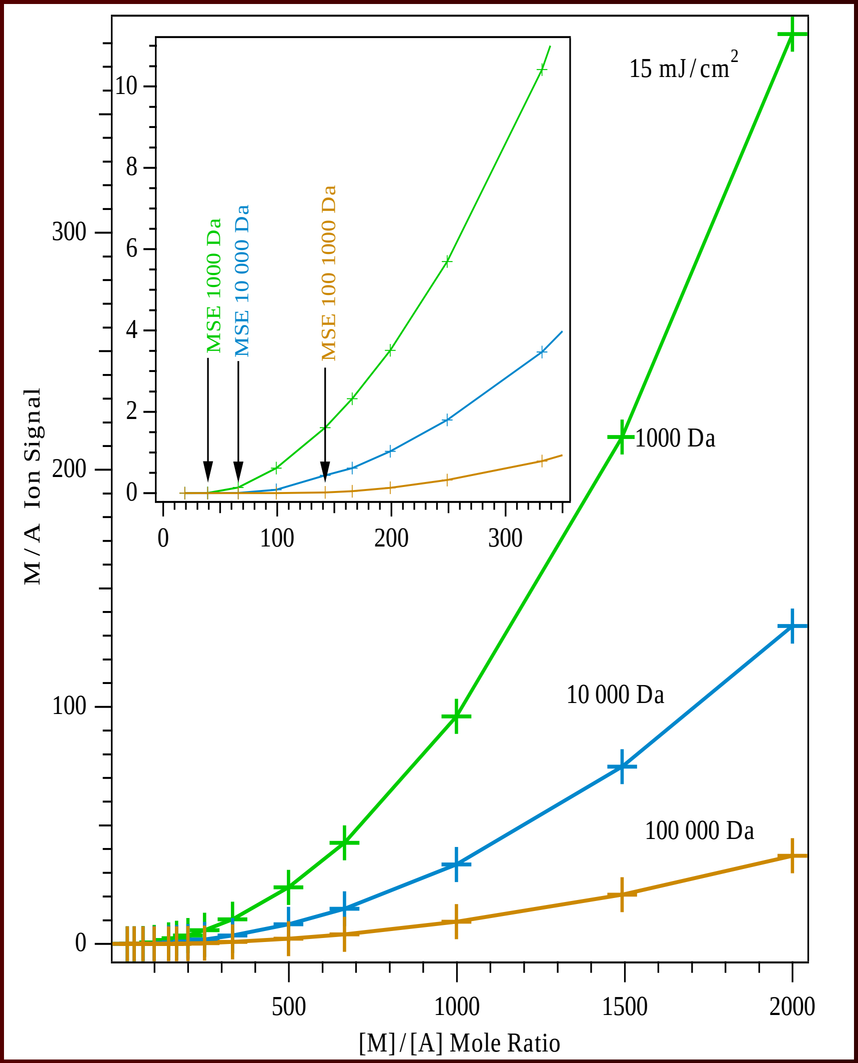


Effect of ΔG on Rates

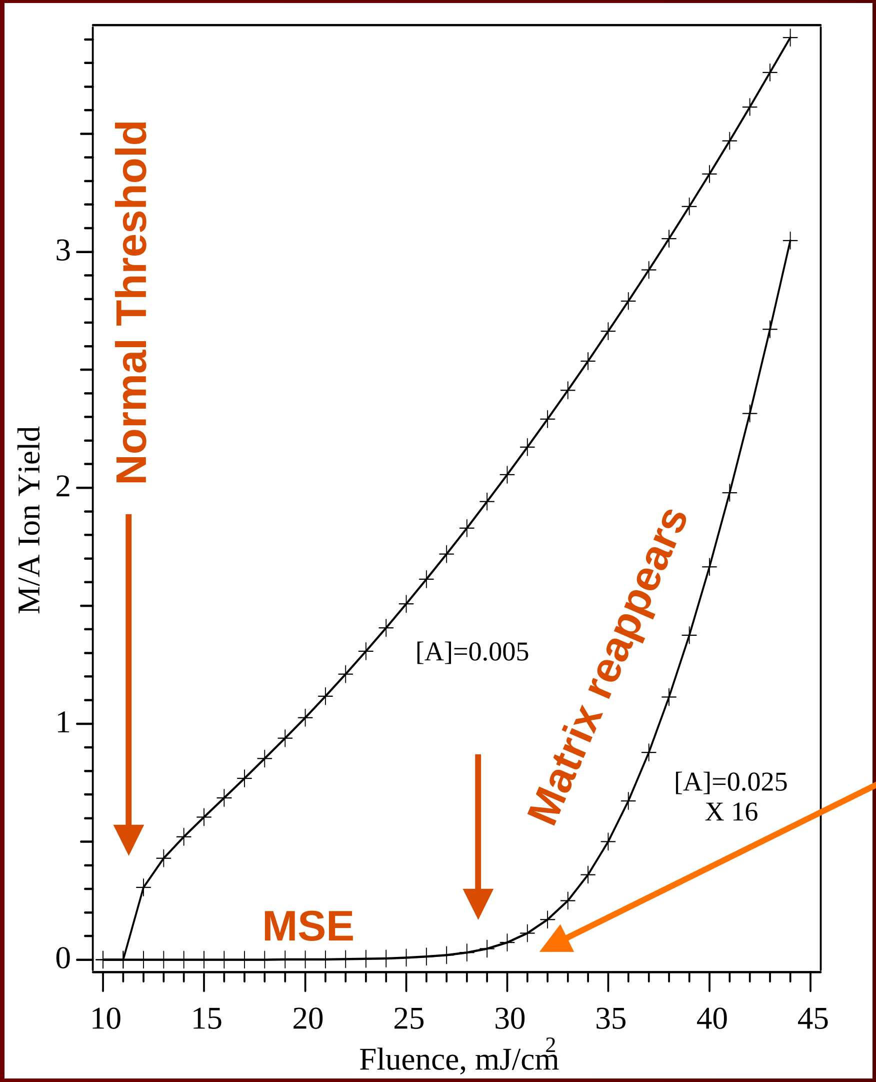


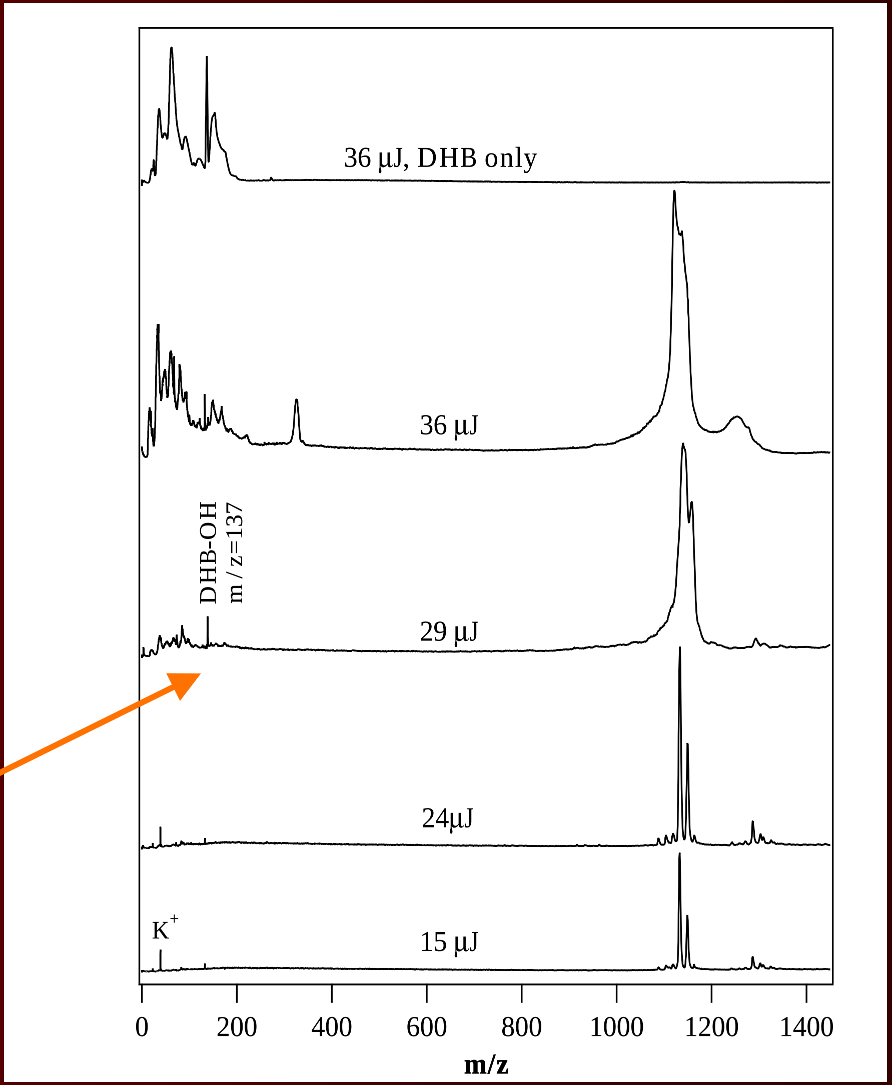
Matrix Suppression Effect vs. MW



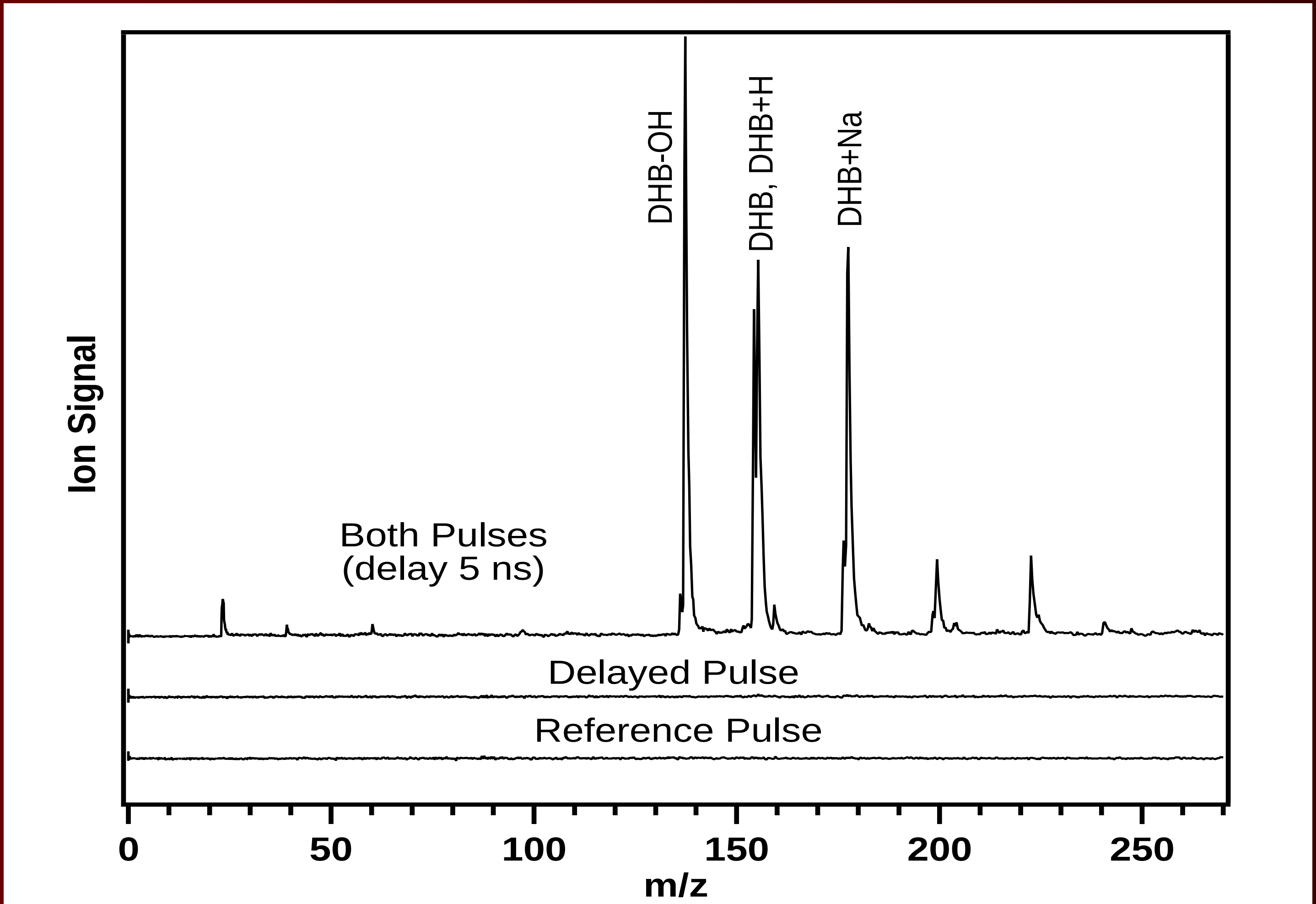


MSE vs. Laser Fluence

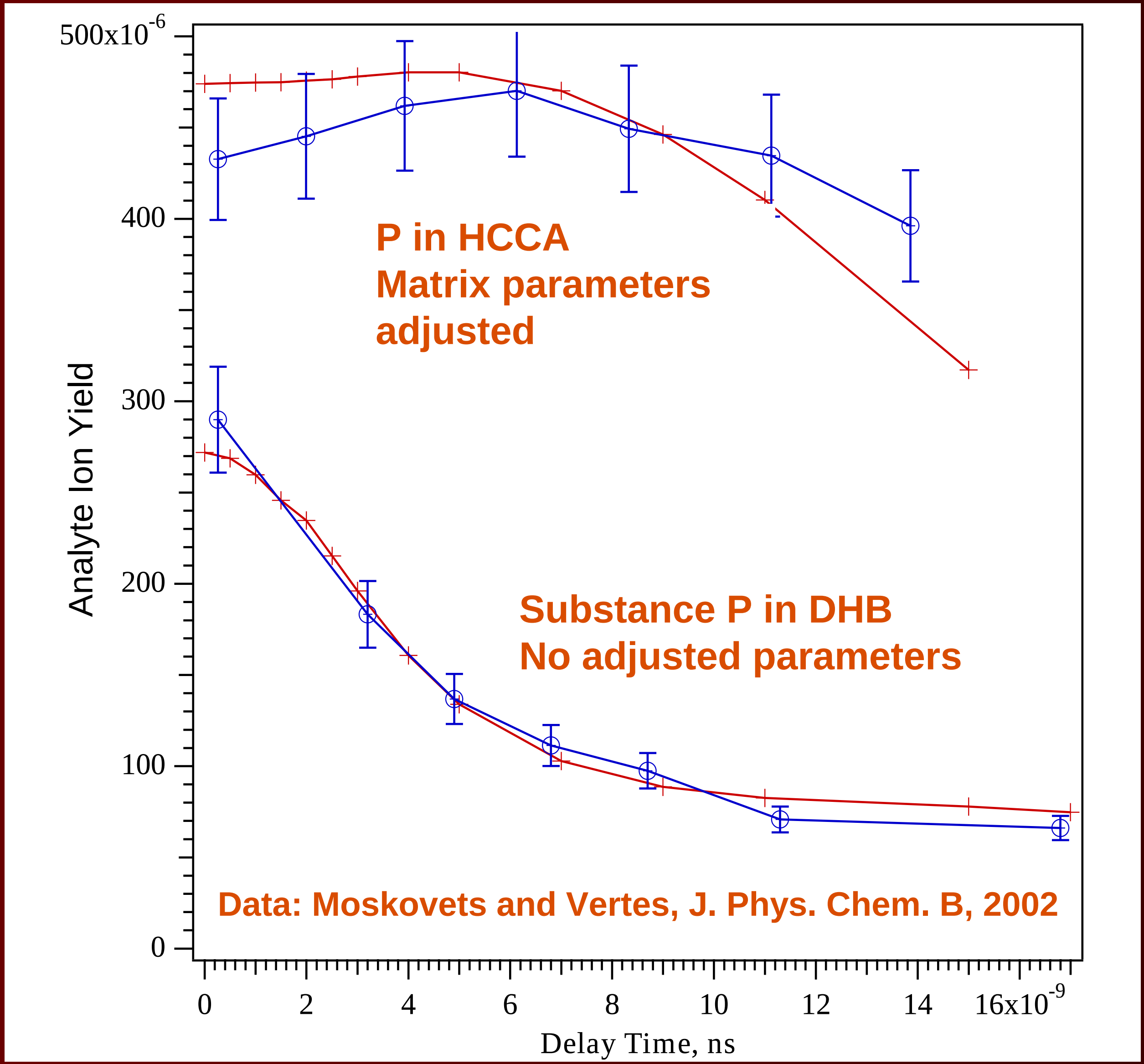




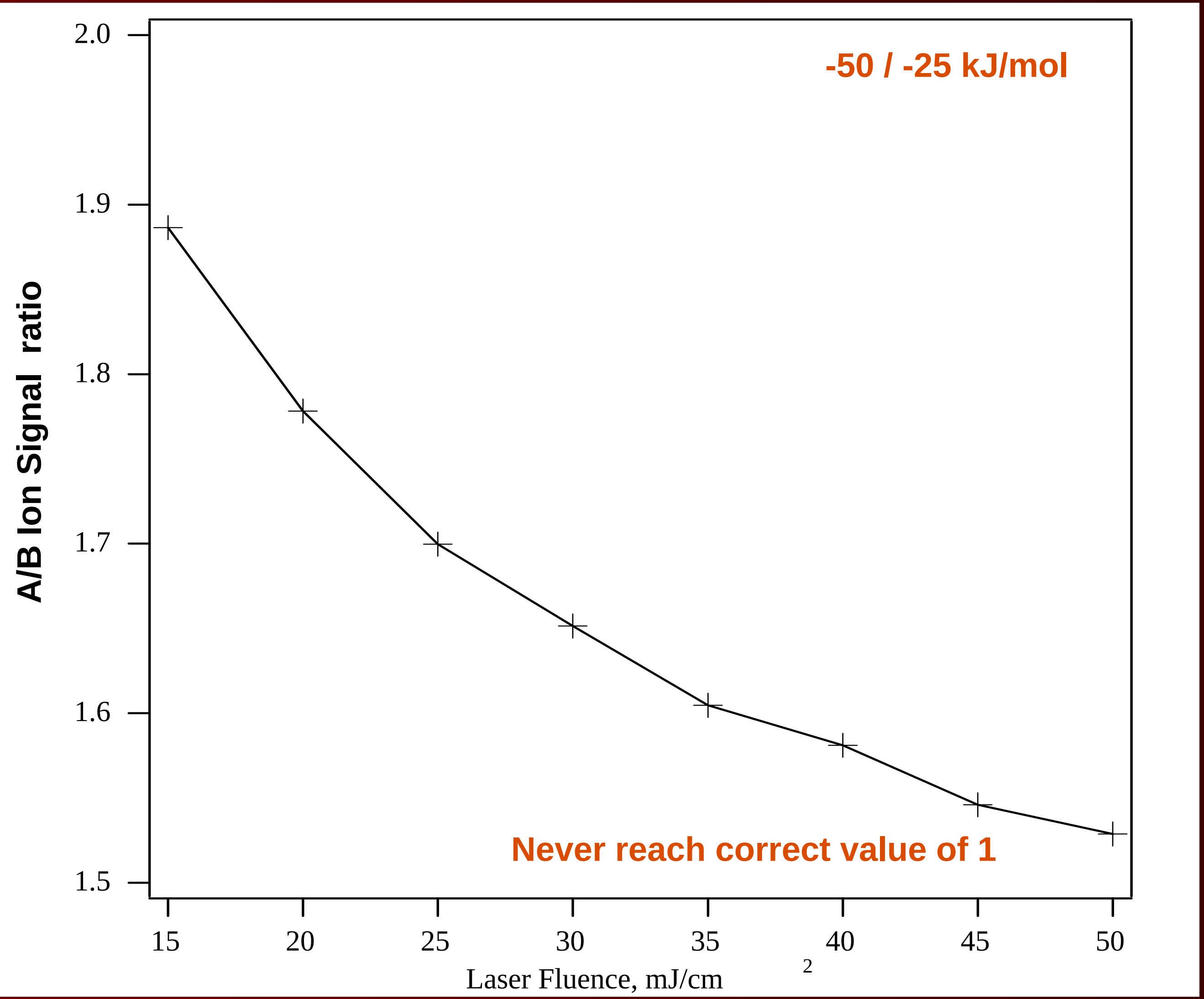
S_1+S_n Exciton Pooling: Time-delayed 2 Pulse Effect



2-Pulse with Analyte



Suppression vs. Fluence



Metal Adduct Reduction Reactions

Metal adduct electron transfer

$AMe^{2+} + M \Rightarrow AMe^{+} + M^{+}$

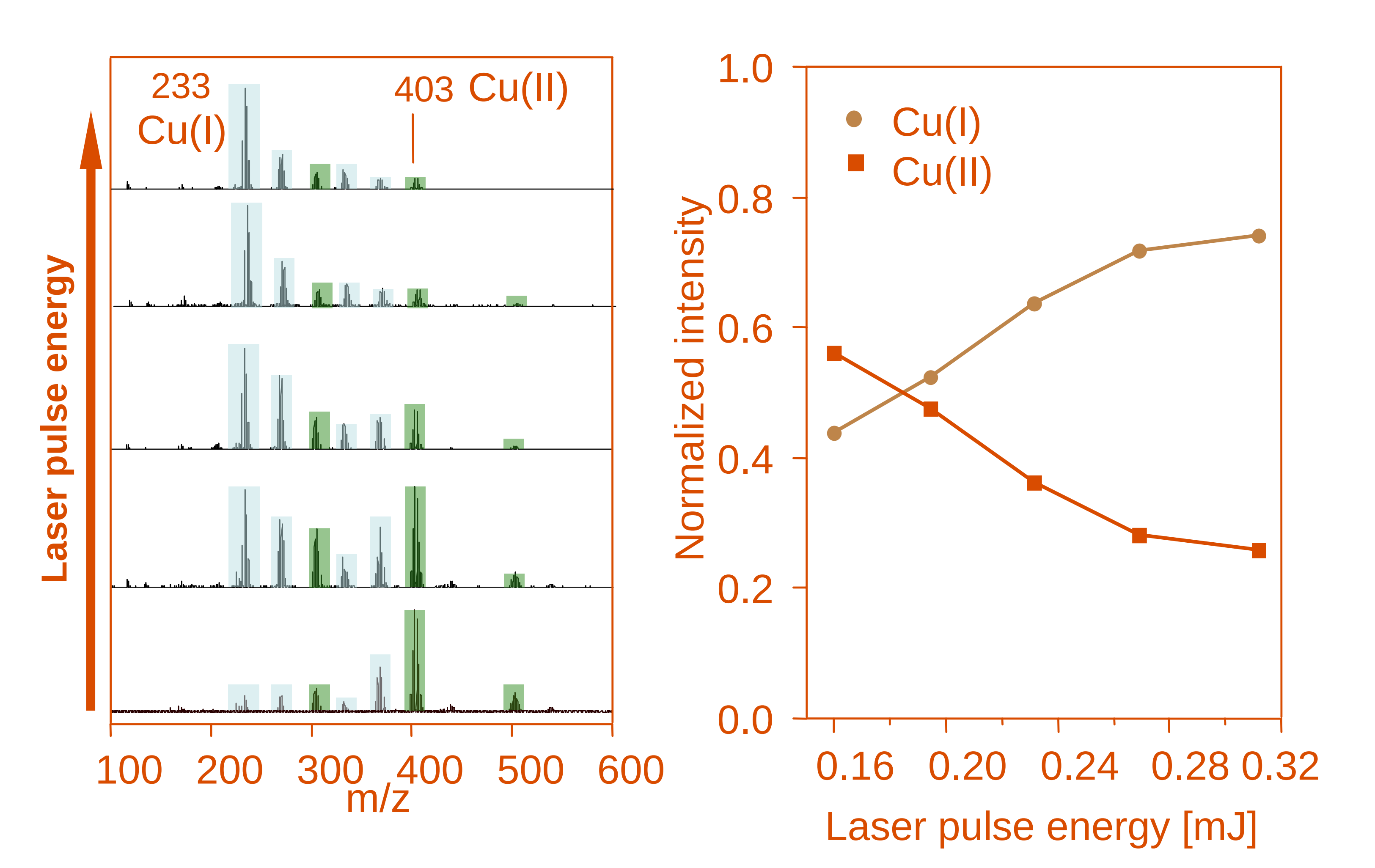
Ionization Potential(M) < IP(Me^{+})

8-9 eV vs 15-20 eV

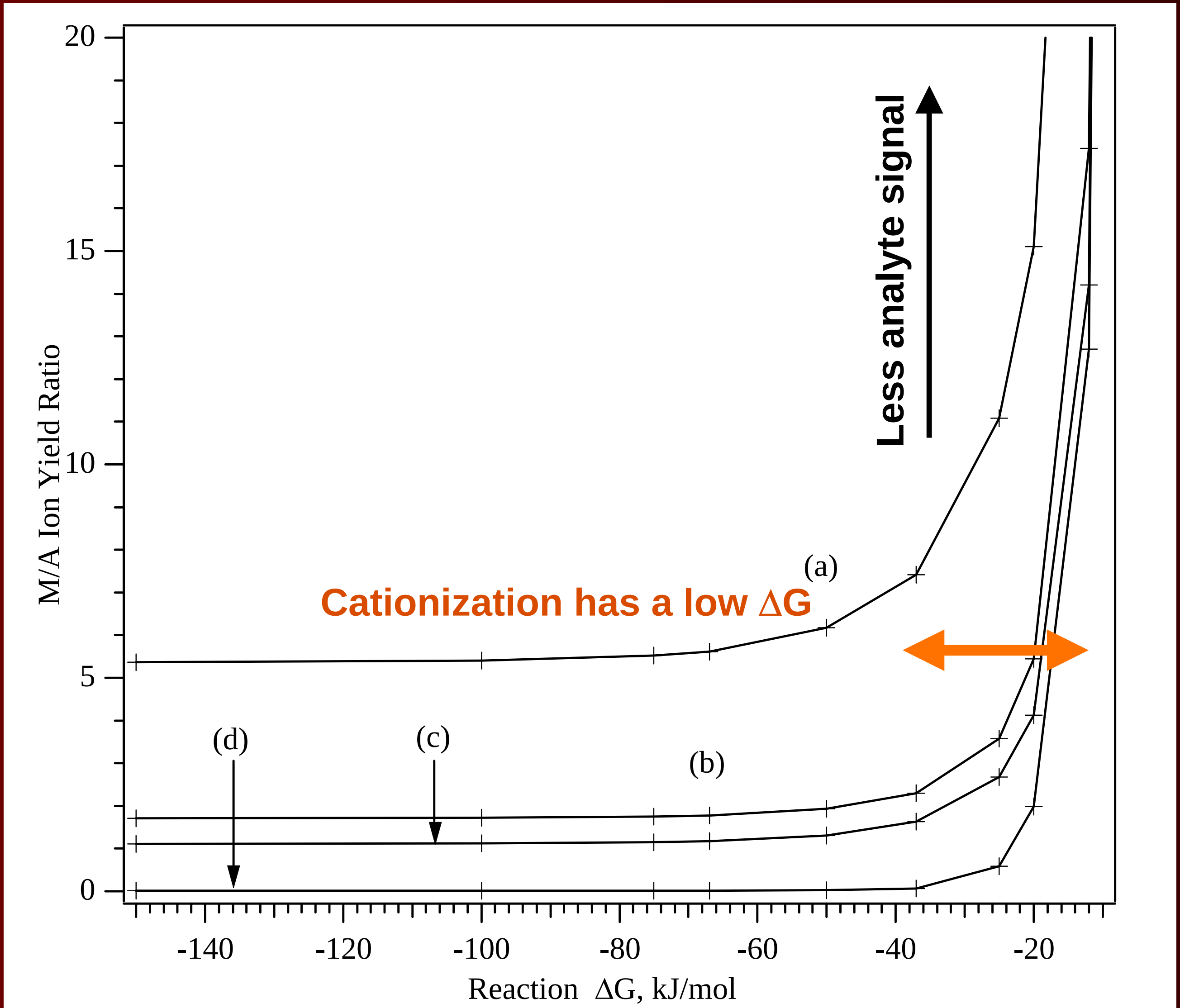
+n ⇨ +1 reactions all exothermic

but +1 ⇨ 0 is endothermic

Divalent Metal Reduction Reactions



Effect of ΔG on Rates



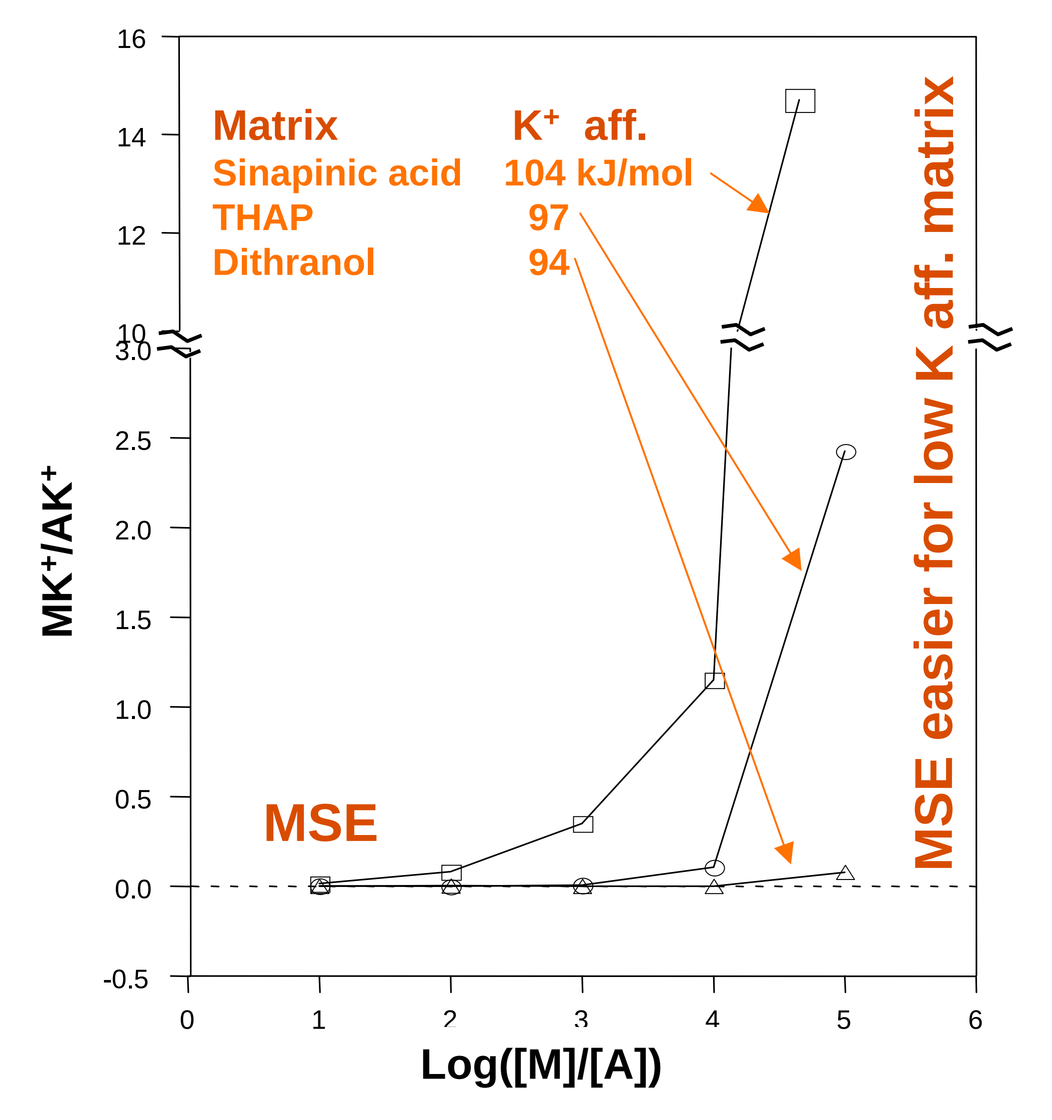
Metal Cationization

Matrix	K^+	Na^+ (EA)	H^+
Nicotinic acid		166 (9)	903 kJ/mol
HCCA		165 (6)	846
3-HPA		163 (8)	896
Ferulic acid		160 (6)	822
Sinapinic acid	104	159 (7)	860
DHB	99	158 (7)	860
THAP	97	154 (5)	878
Dithranol	94	150 (6)	874
3-AQ		144 (6)	

Analyte	Na^+
dipeptides	>160 kJ/mol
nucleobases	165-190
carbohydrates	>160

Depending on matrix, 0 to 40 kJ/mol Na^+ transfer exothermicity

MSE by Metal Cationization

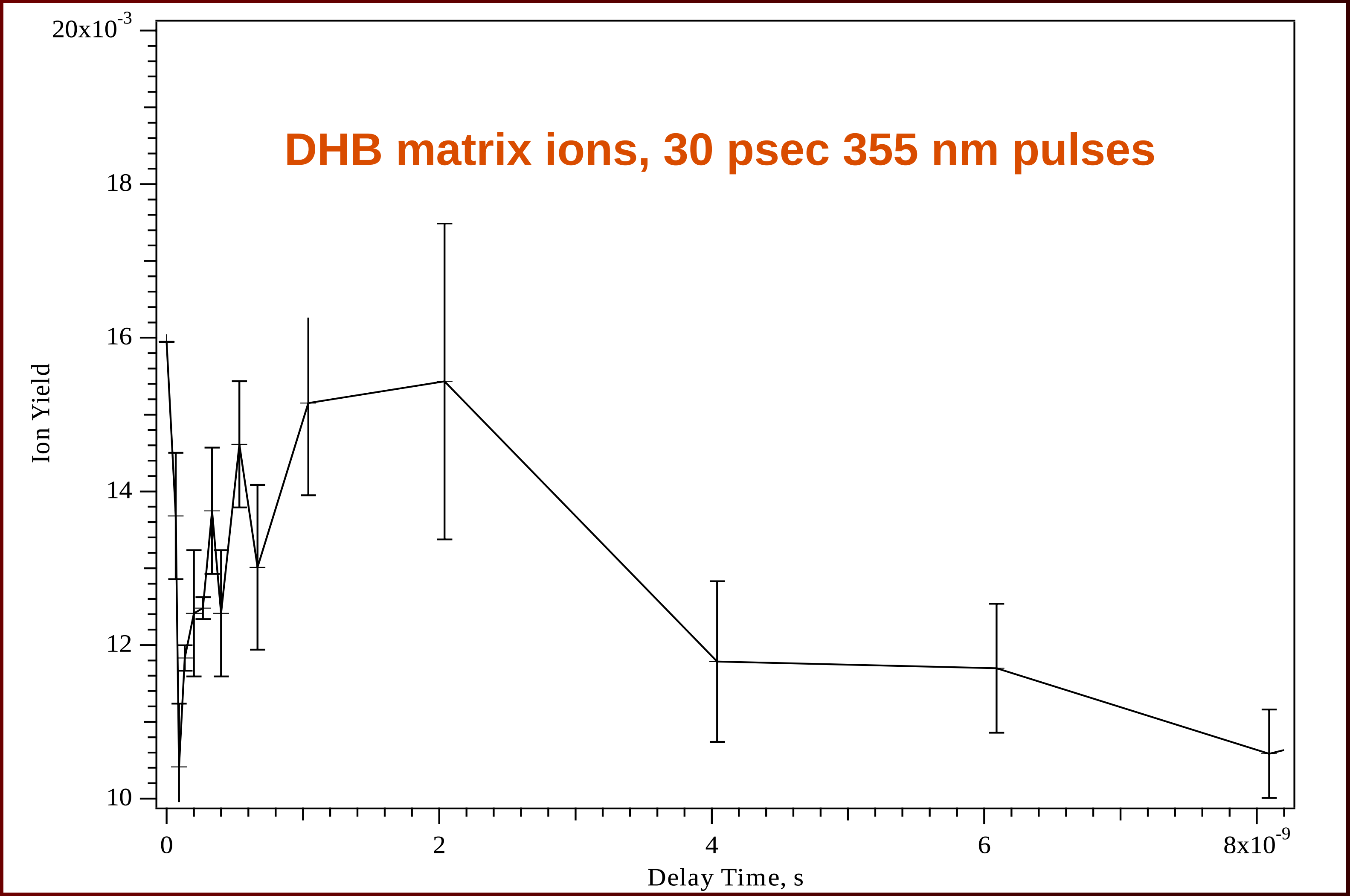


Model Results, Matrix & Analyte

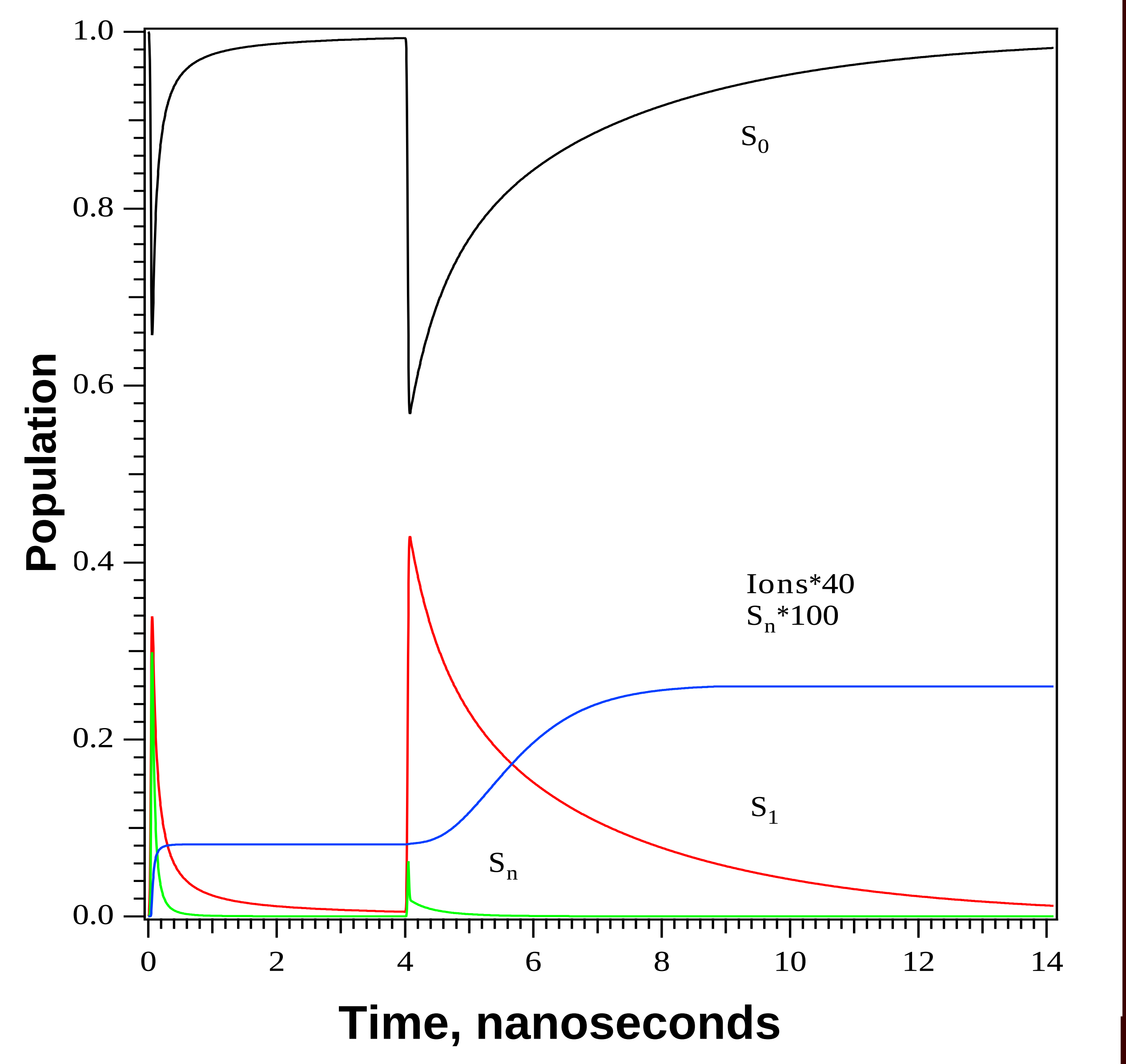
- Existence of MSE + ASE
- Characteristics of MSE + ASE vs.:
  - Molecular weight
  - Fluence
  - Concentration- absolute & relative
  - ΔG
- 2-Pulse effect with analyte
- Quantification of cationization vs. protonation
- Quantification of ion suppression effects
- Rational matrix choice for desired analyte

- Wide-ranging quantitative agreement with data.
- Predictive capability.

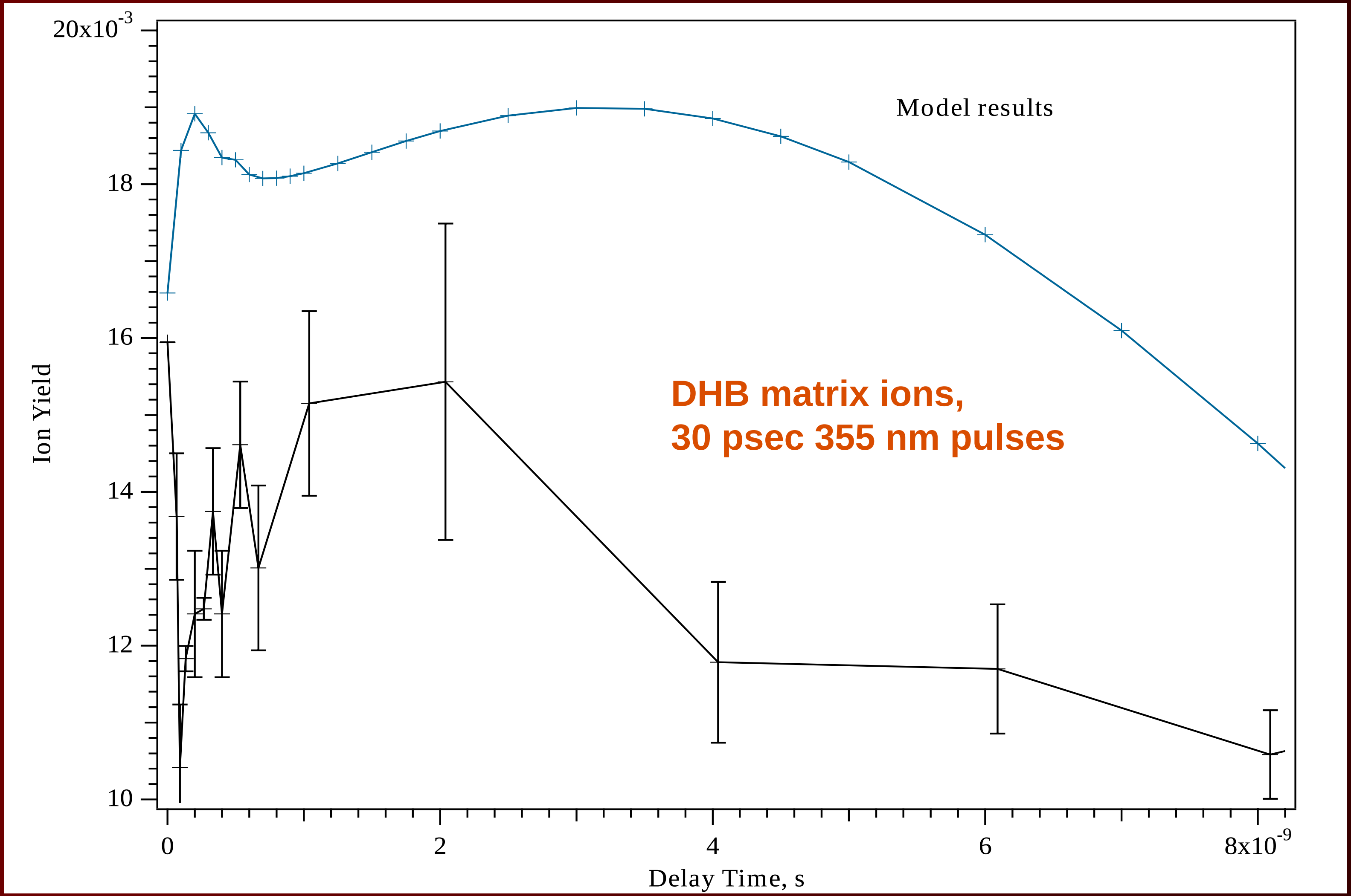
S_1+S_n Exciton Pooling: Time-delayed 2 Pulse Effect



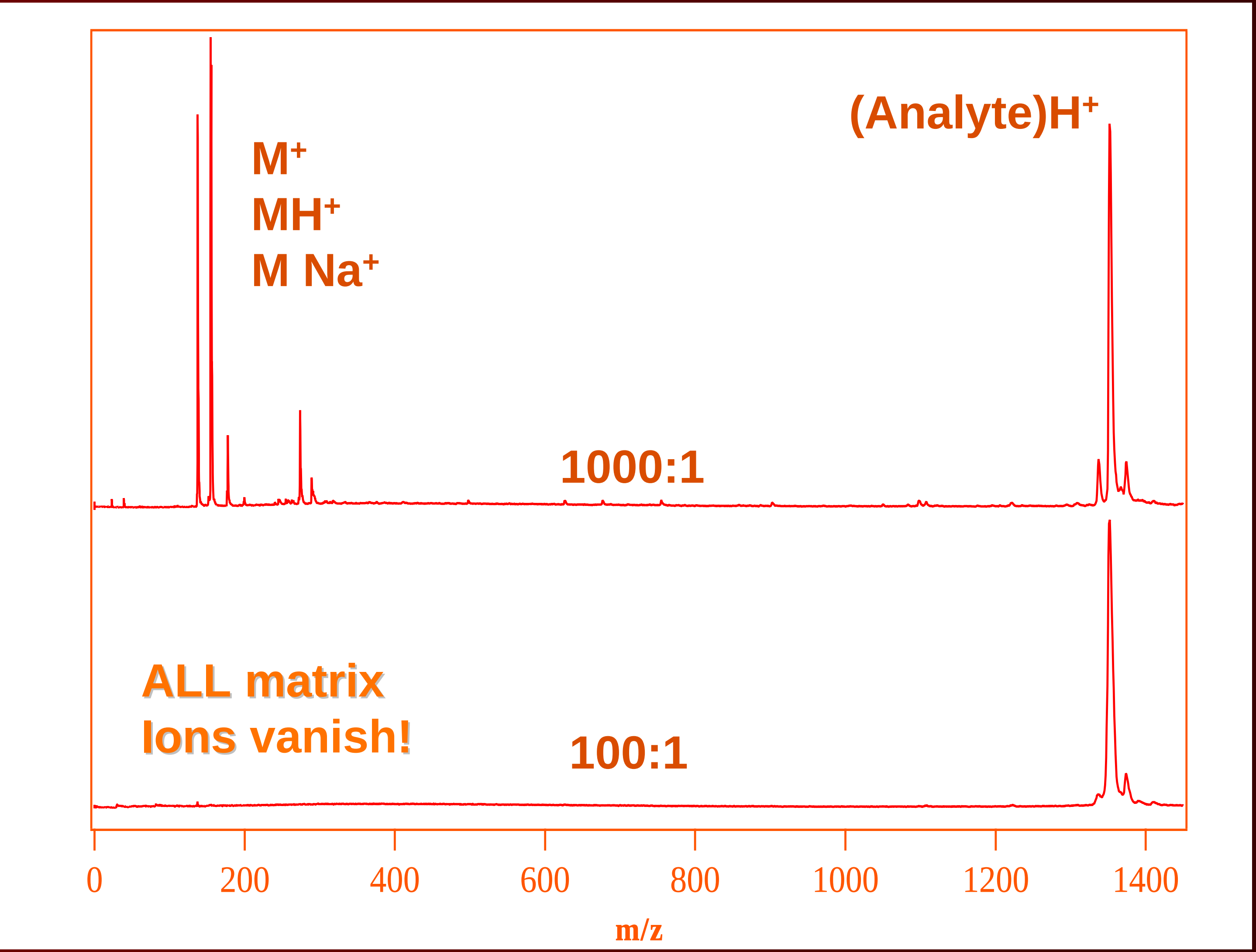
Example Results, 2 Pulses



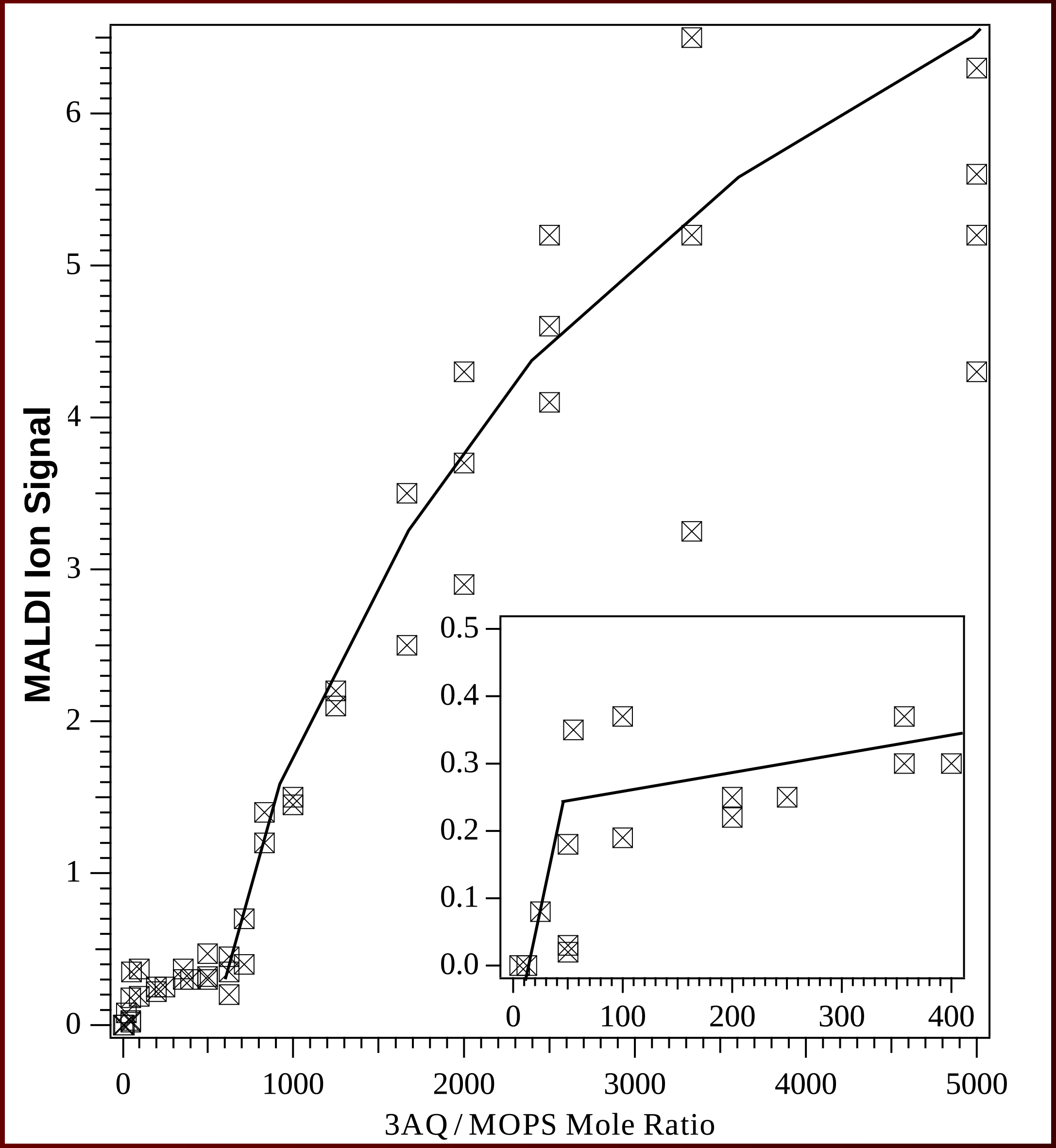
S_1+S_n Exciton Pooling: Time-delayed 2 Pulse Effect



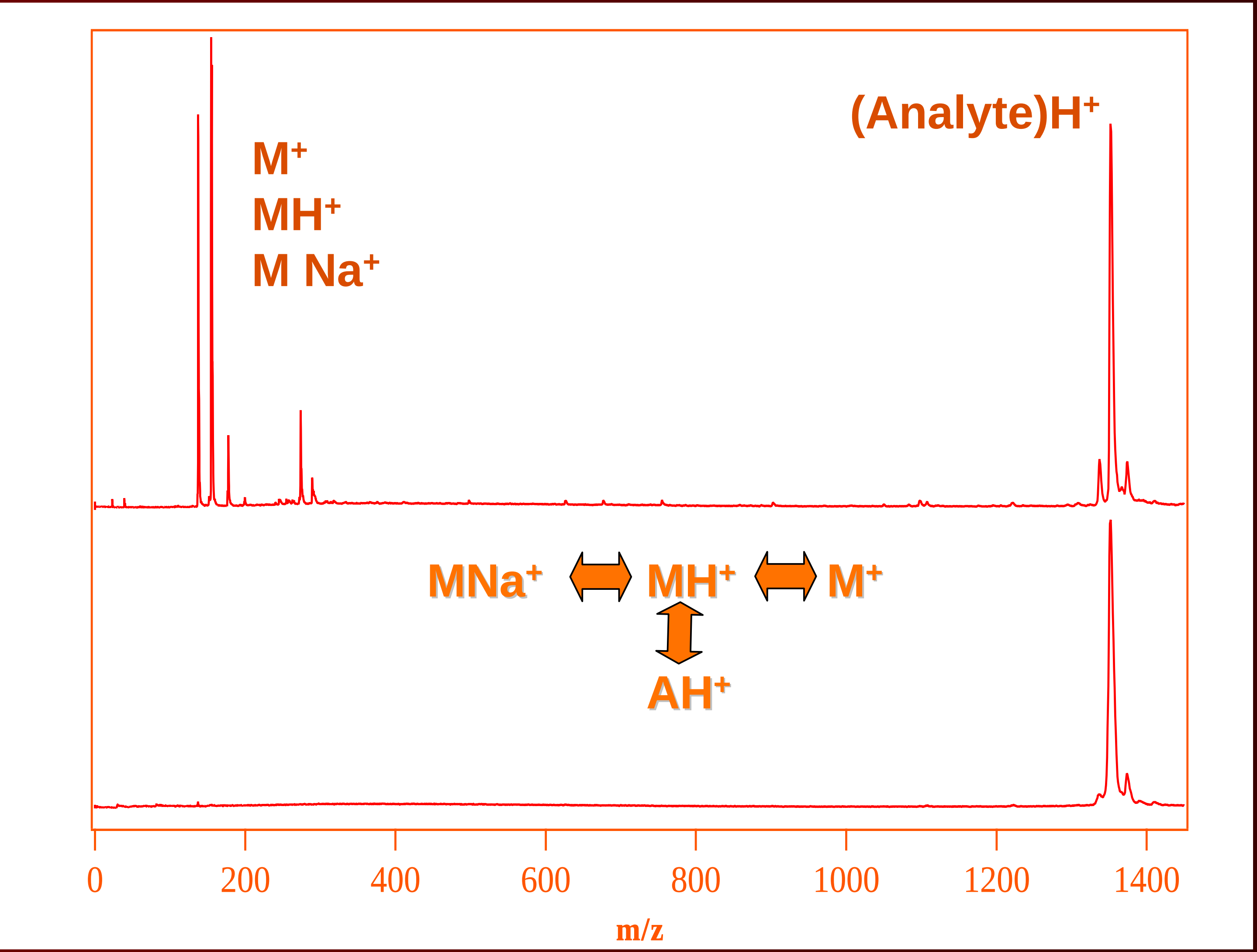
Matrix Suppression Effect: Dissimilar Ions



Matrix Suppression Effect



Matrix Suppression Effect: Dissimilar Ions



Interconversion Reactions

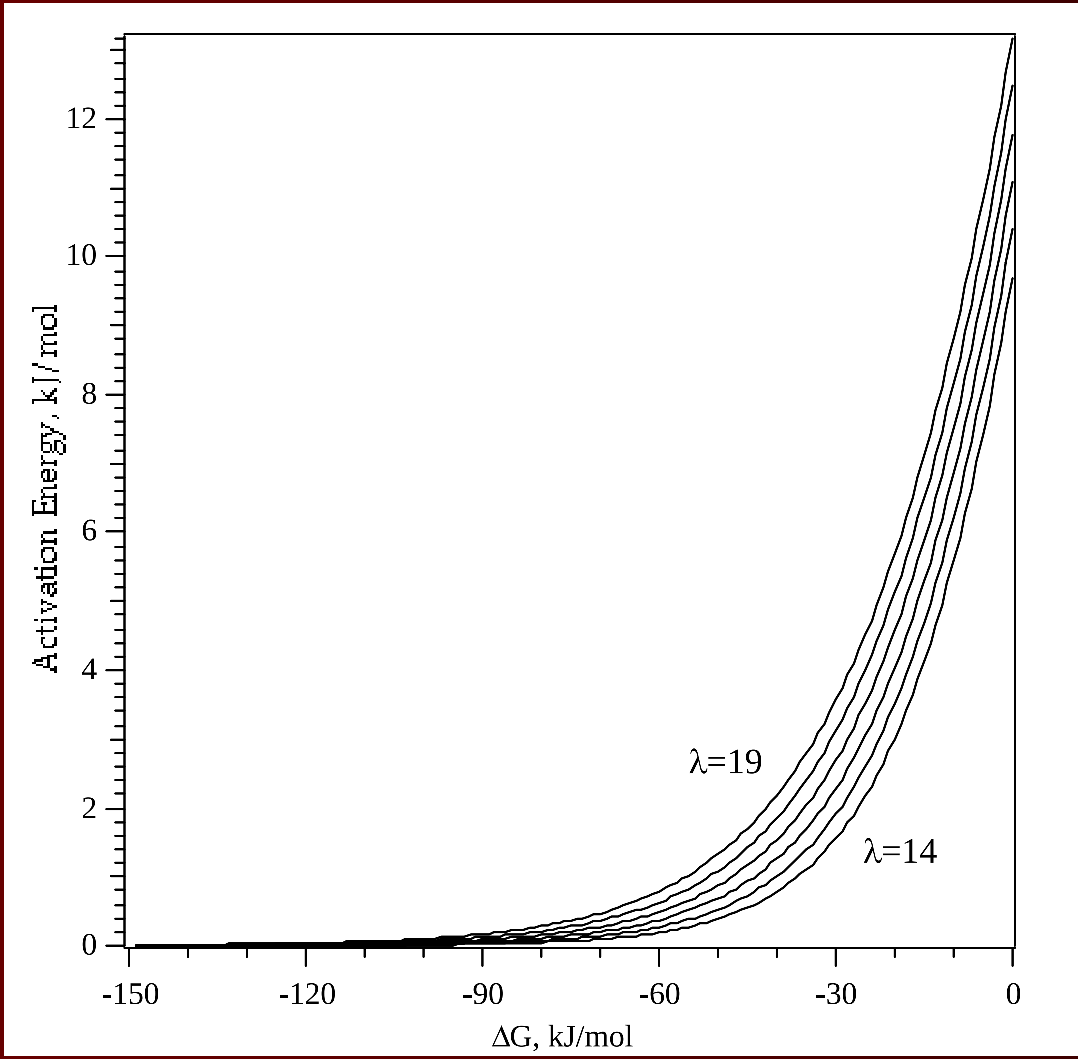
$MH^+ + M \Leftrightarrow M^+ + M\text{-}H$ 35 kJ/mol

$MNa^+ + M \Leftrightarrow MH^+ + (M\text{-}H)Na$ -43 kJ/mol

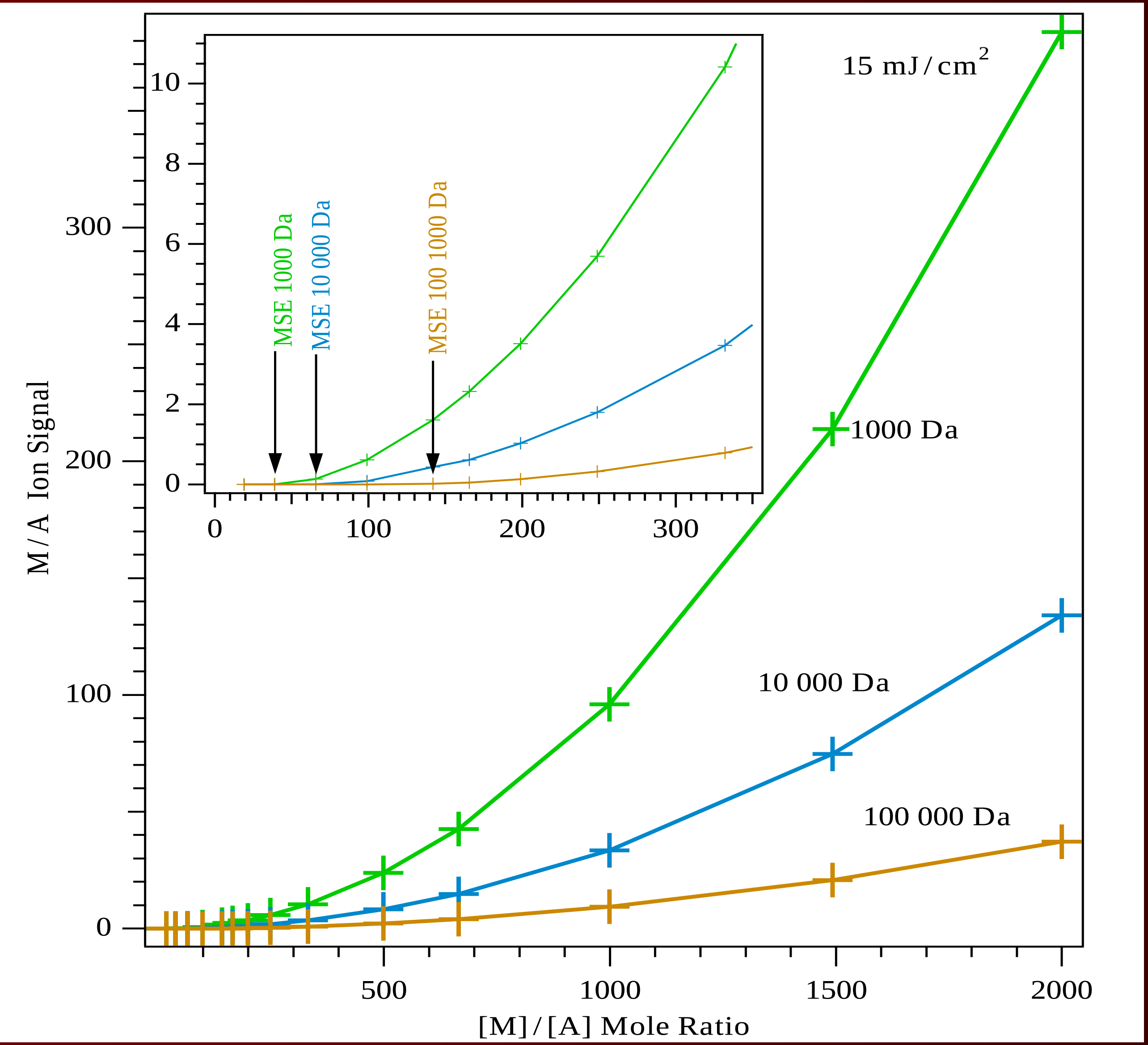
$MNa^+ \Leftrightarrow MH^+ \Leftrightarrow M^+$

Low energy, facile in plume

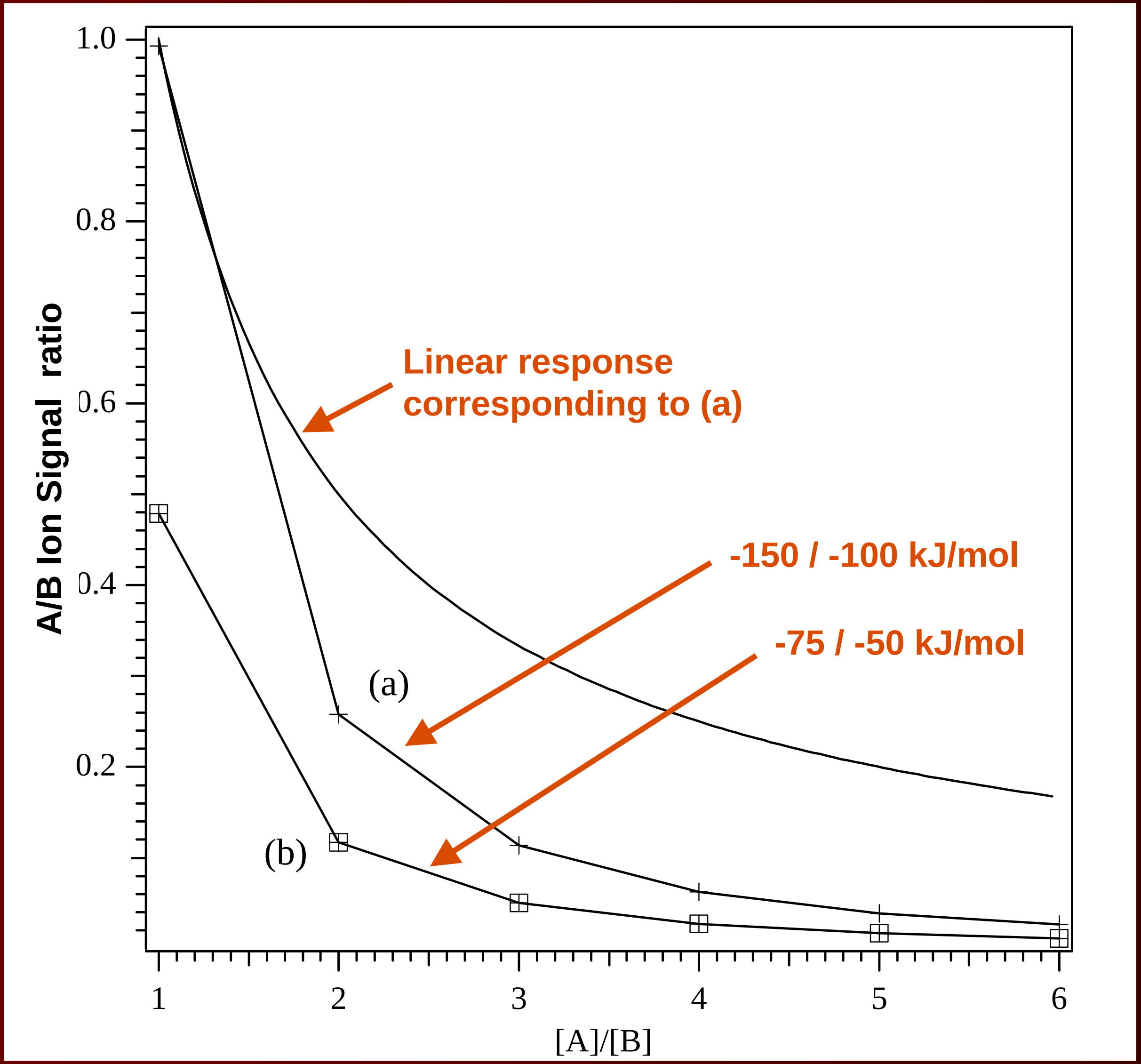
Activation Energy vs. ΔG and Lambda



Matrix Suppression Effect



Suppression vs. Concentration



The Current Picture of UV-MALDI

1) Primary (matrix) & secondary (analyte) ionization steps

2) Secondary ionization: ion-molecule thermodynamics & kinetics

3) We can calculate & predict most of it