Biokinetics & TAC fitting

Biokinetics & TAC fitting

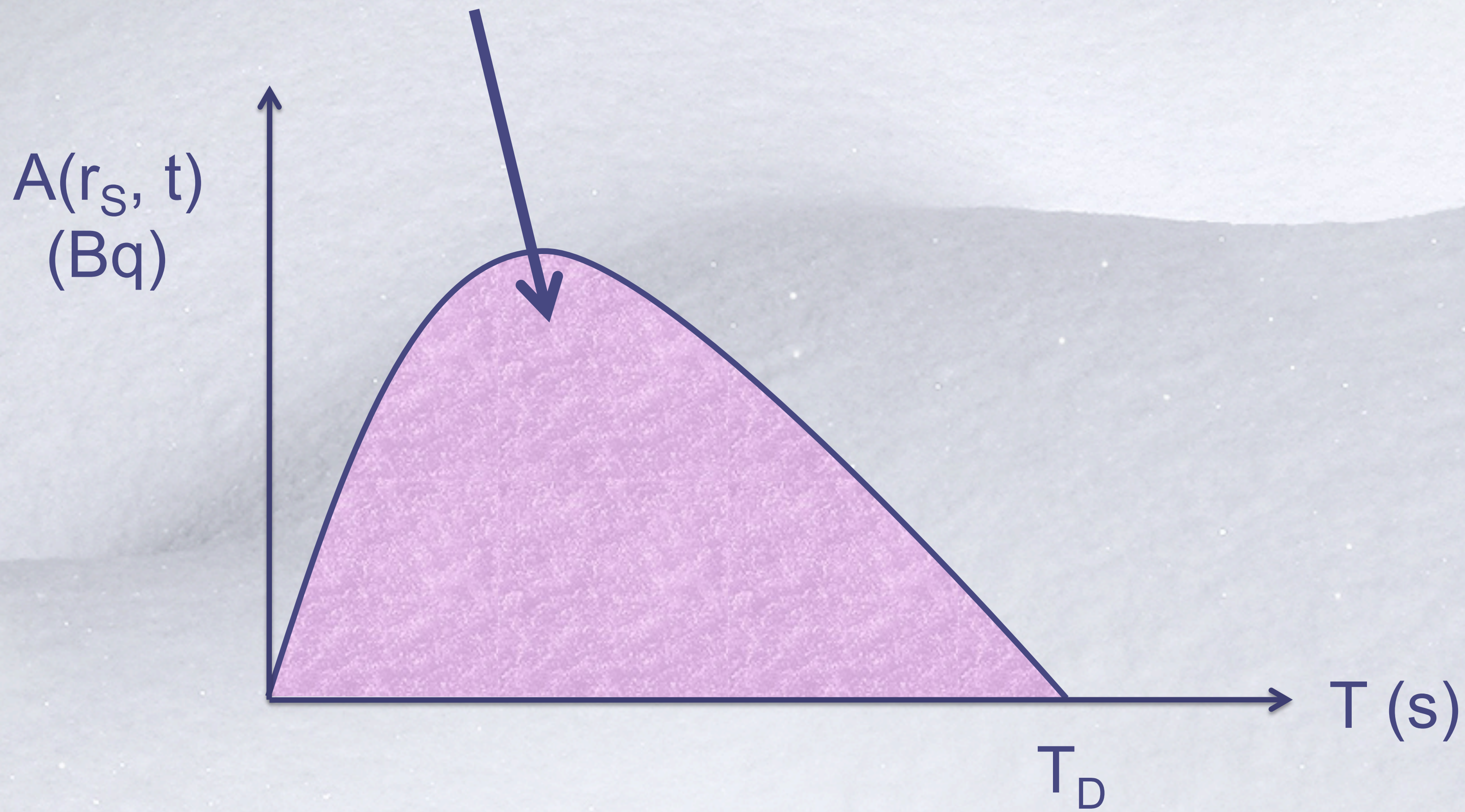
$$D\left(r_T, T_D\right) = \sum_{r_S} \tilde{A}\left(r_S, T_D\right) S\left(r_T \leftarrow r_S\right)$$

$$\tilde{A}\left(r_S, T_D\right)$$

- "Time-integrated activity"
  - In source region R_S
  - Over dose-integration period T_D
- Formerly: cumulated activity $\tilde{A}_h$
- Expressed in Bq.s: [Trans.s^{-1}.s]=[Trans]

Time-integrated activity

$$\tilde{A}\left(r_S, T_D\right) = \int_0^{T_D} A(r_S, t)\, dt$$

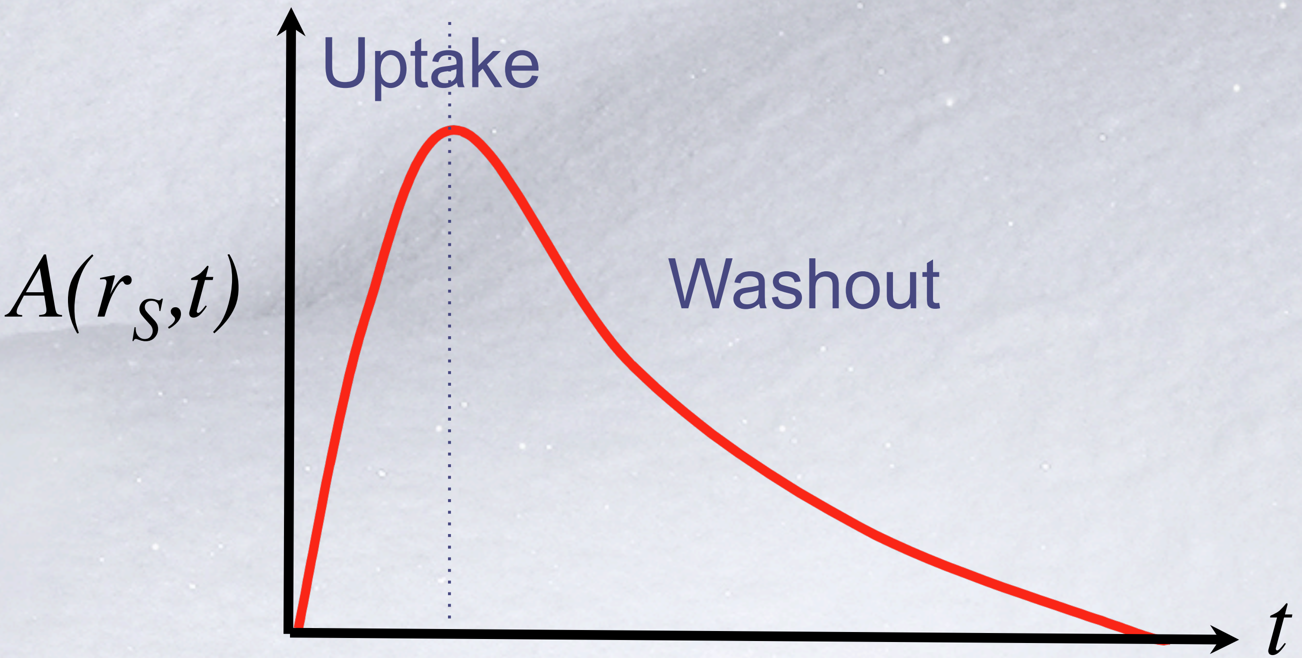


Variation of activity in r_S with time

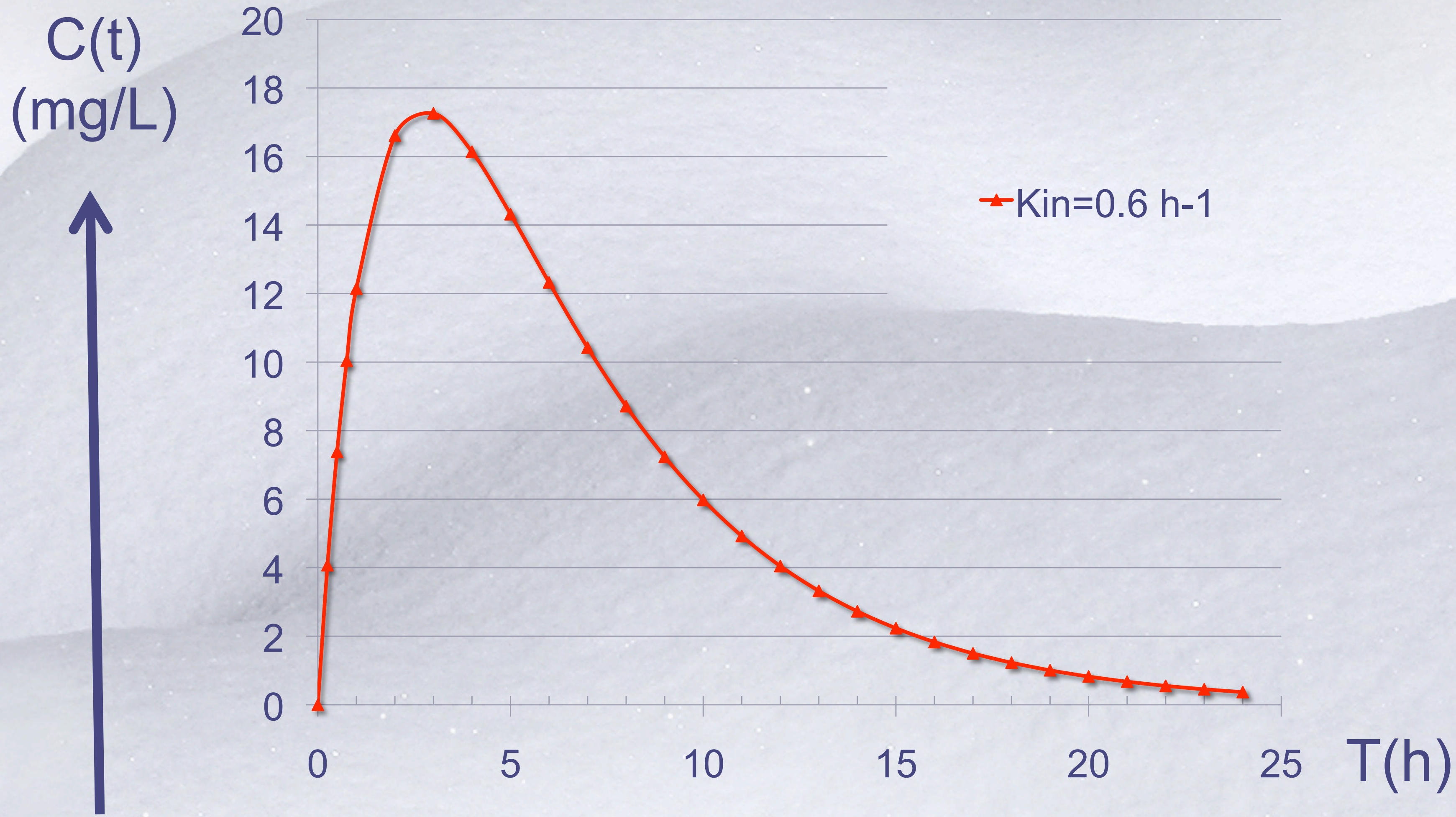
General situation:

- Uptake phase
- Washout phase

+ « normal » radioactivity decay with T_{phy}



Example:



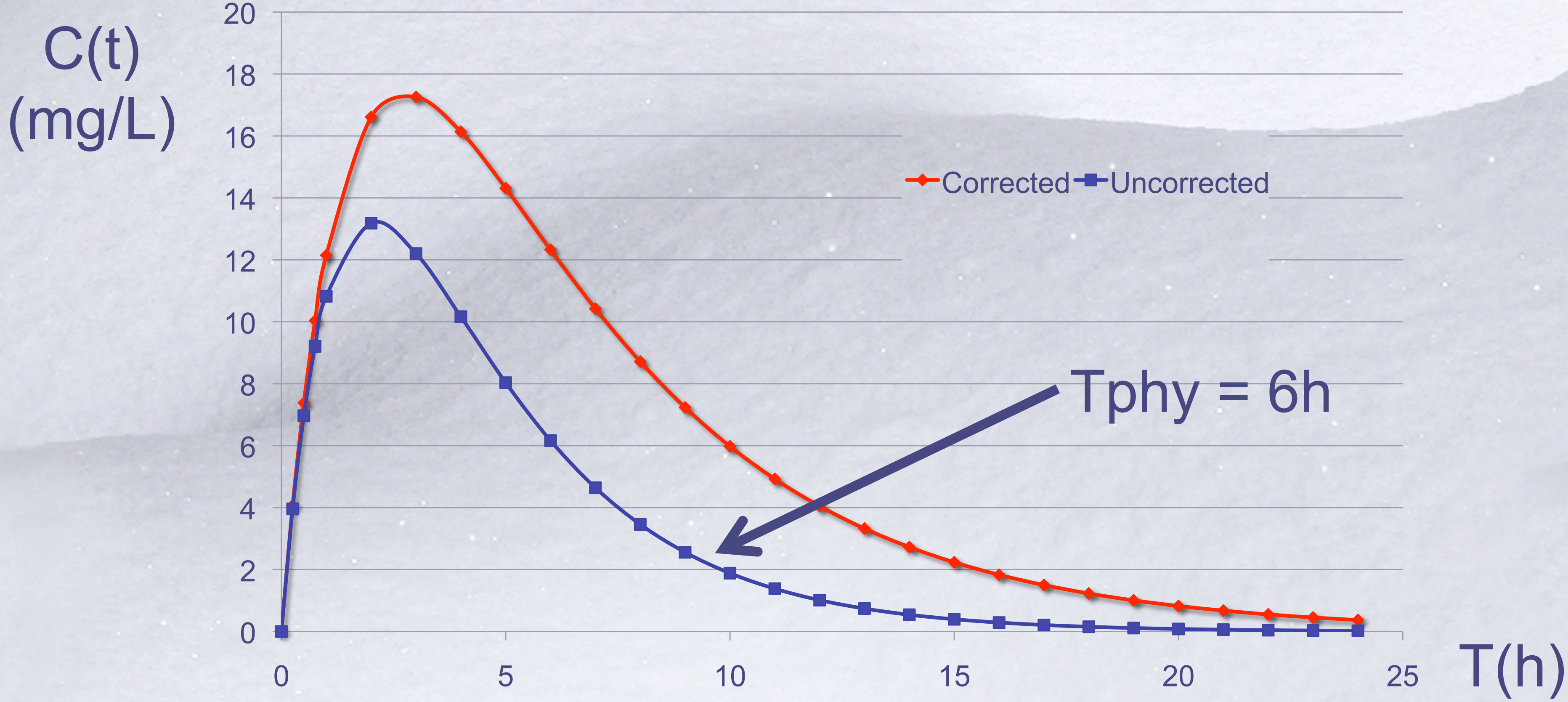
Temporal variation of *drug* concentration

Example:

If the drug is labelled with a radioactive isotope,

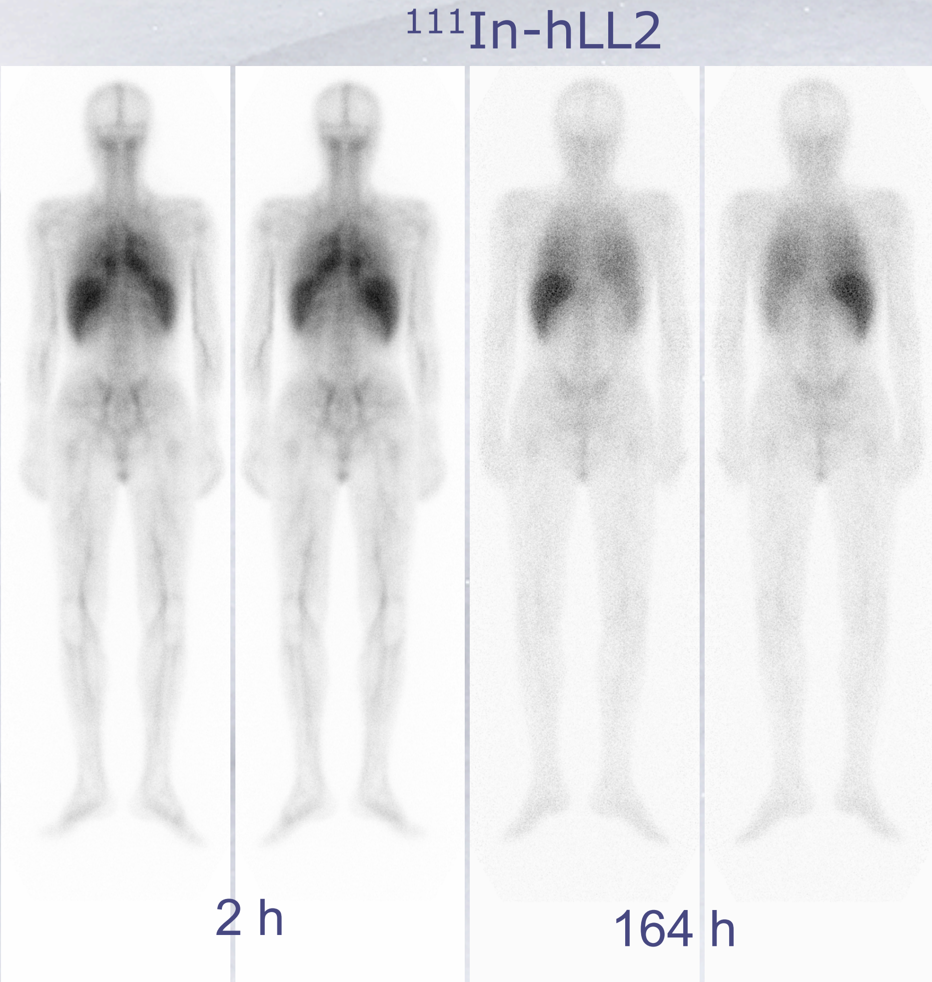
what is detected/measured: activity

Need to take into account radioactive decay!



Quantitative imaging:

Measure/calculation of the *activity*.



This is what is needed for dosimetry…

Blood sampling:

Measure/calculation of the *drug concentration:*

- One calibration sample (i.e. X MBq at day 0)
- Several blood samples taken at day 1, 2, etc.
- All samples are read the same day (i.e. day 8)

What is measured is the *biologic* behaviour of the compound (it is implicitly decay-corrected)

For dosimetry calculation, one should “un-correct” for radioactive decay…

Effective half-life

If the measured activity decreases exponentially:

$T_{Eff} = Ln2/\lambda_{Eff}$ is the *effective* half-life

$$A(r_S,t) = A_0 \times e^{-\lambda_{Bio} t} \times e^{-\lambda_{Phy} t}$$

$$= A_0 \times e^{-(\lambda_{Bio} + \lambda_{Phy})t}$$

$$= A_0 \times e^{-\lambda_{Eff} t}$$

With: $$\frac{1}{T_{Eff}} = \frac{1}{T_{Bio}} + \frac{1}{T_{Phy}}$$

And $$\tilde{A}(r_S,\infty) = \frac{T_{Eff}}{Ln2} \times A_0 = 1.443 \times A_0 \times T_{Eff} = \frac{A_0}{\lambda_{Eff}}$$

Effective half-life

General situation

$$A = \sum_j A_j \times e^{-(\lambda_j + \lambda_{Phy})t}$$

T_{Eff}

With:

$$\frac{1}{\left(T_j\right)_{Eff}} = \frac{1}{T_j} + \frac{1}{T_{Phy}}$$

And:

$$\tilde{A}\left(r_S, \infty\right) = 1.443 \sum_j A_j \left(T_j\right)_{Eff}$$

Playing with T_{Eff}

$$\frac{1}{T_{Eff}} = \frac{1}{T_{Bio}} + \frac{1}{T_{Phy}}$$

- T_{Eff} is ALWAYS smaller than the smallest half-life

  Ex: T_{Phy} = 8d, T_{Bio} = 2d T_{Eff} =1.6d

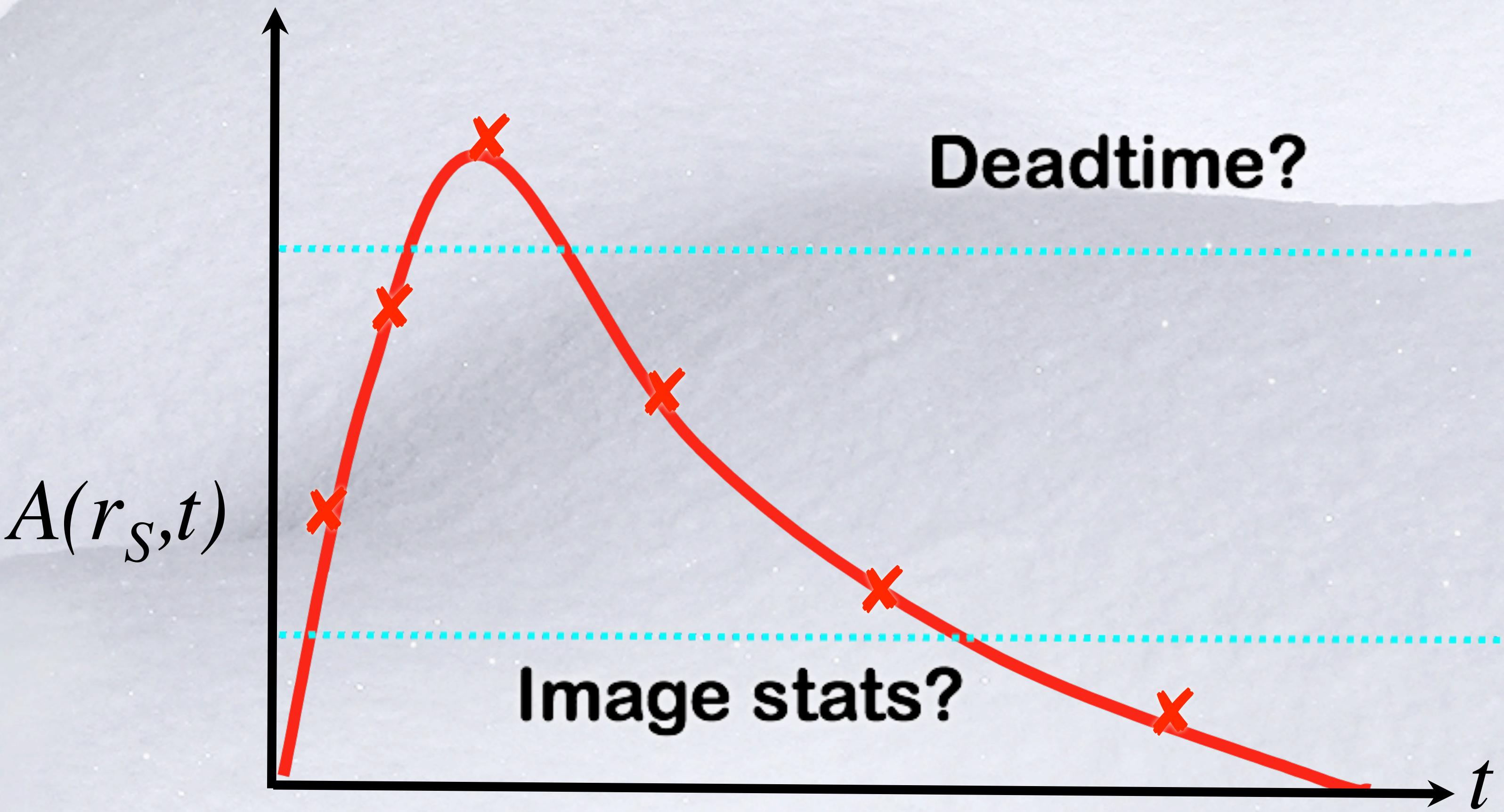
- If $T_{Bio} >> T_{Phy}$ T_{Eff} -> T_{Phy}

  and vice-versa:

- If $T_{Bio} << T_{Phy}$ T_{Eff} -> T_{Bio}

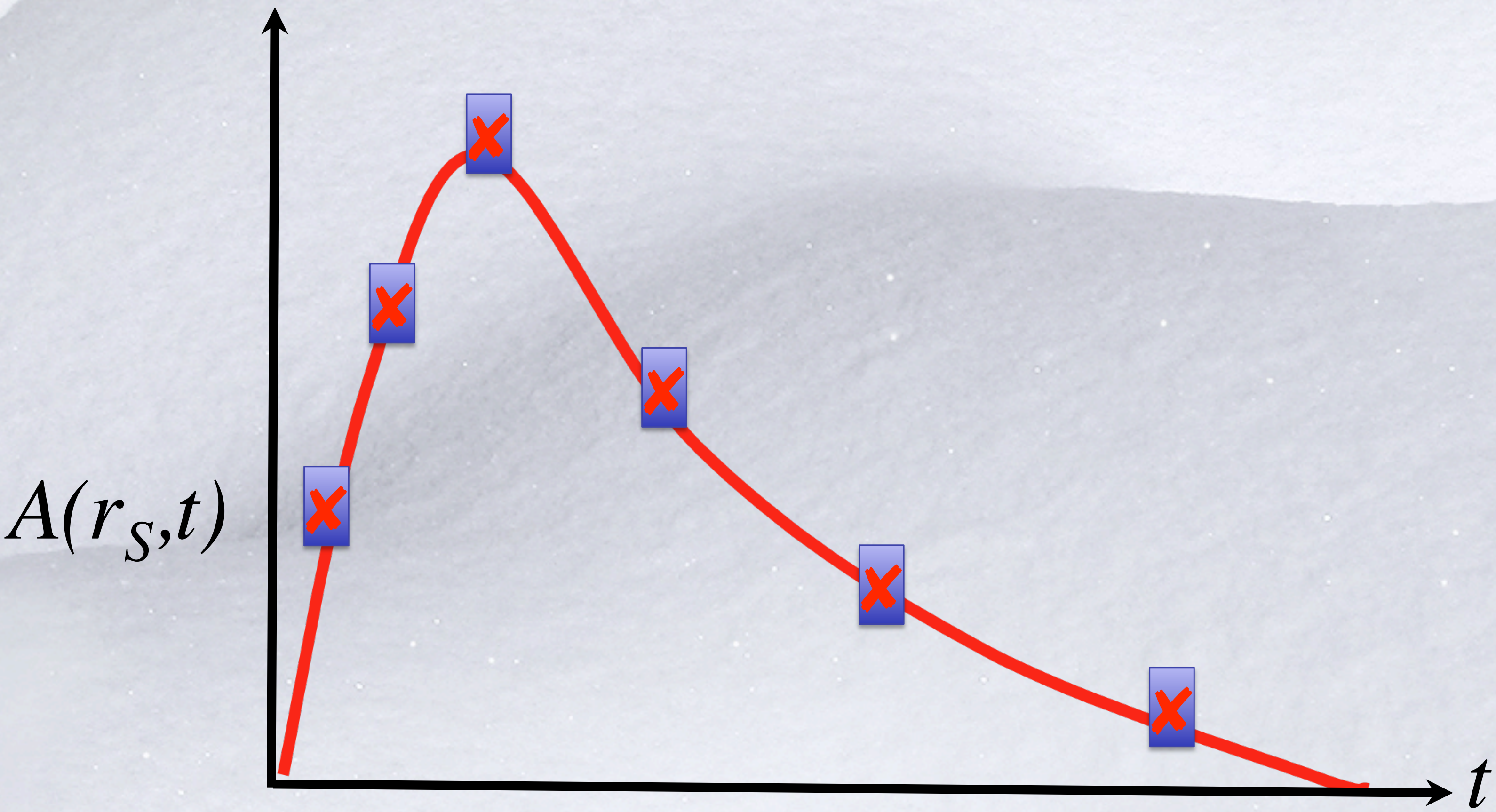
Time-integrated activity

Quantitative Imaging at ≠ time-points...



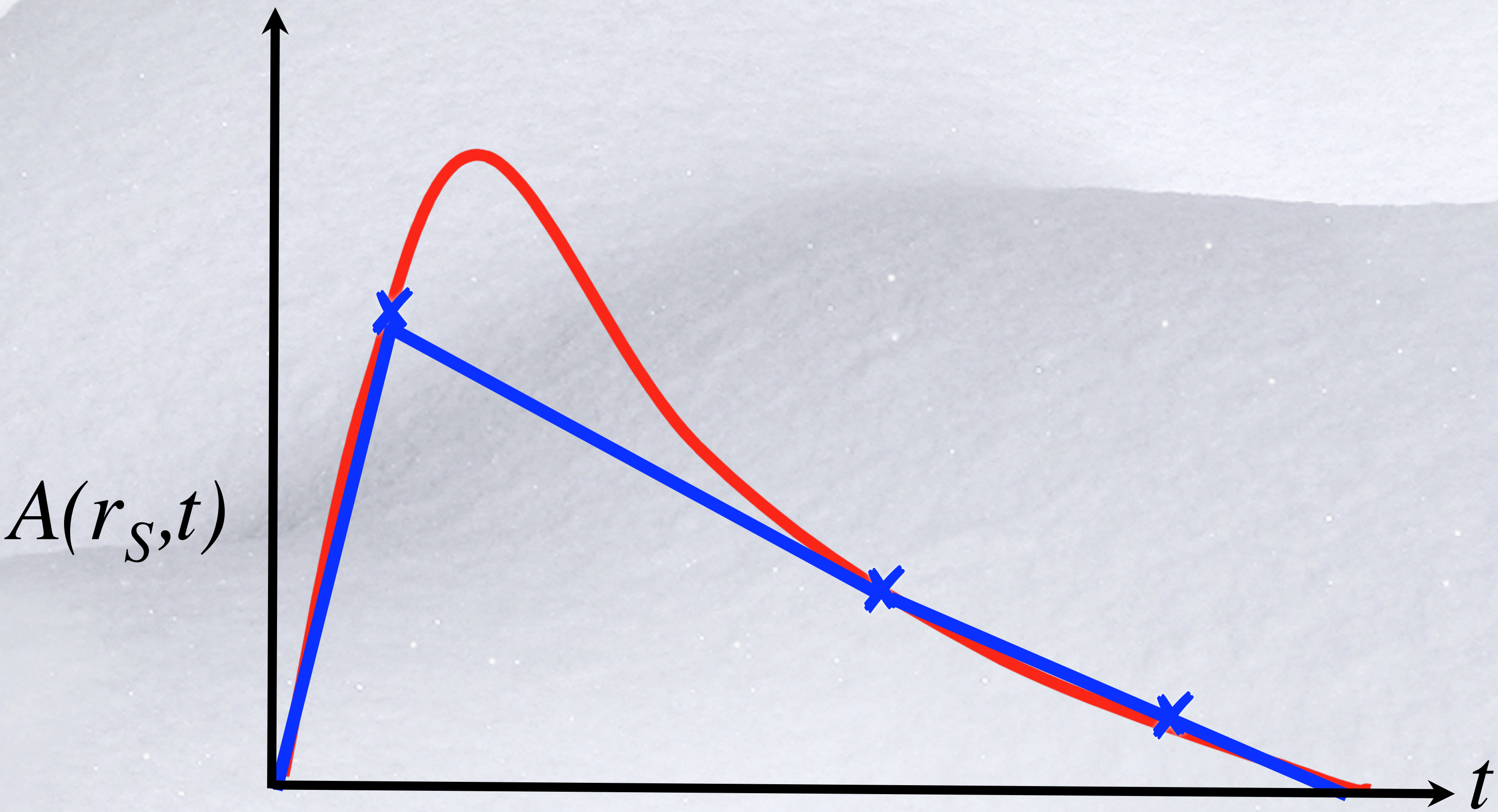
Time-integrated activity

- Importance of temporal sampling...



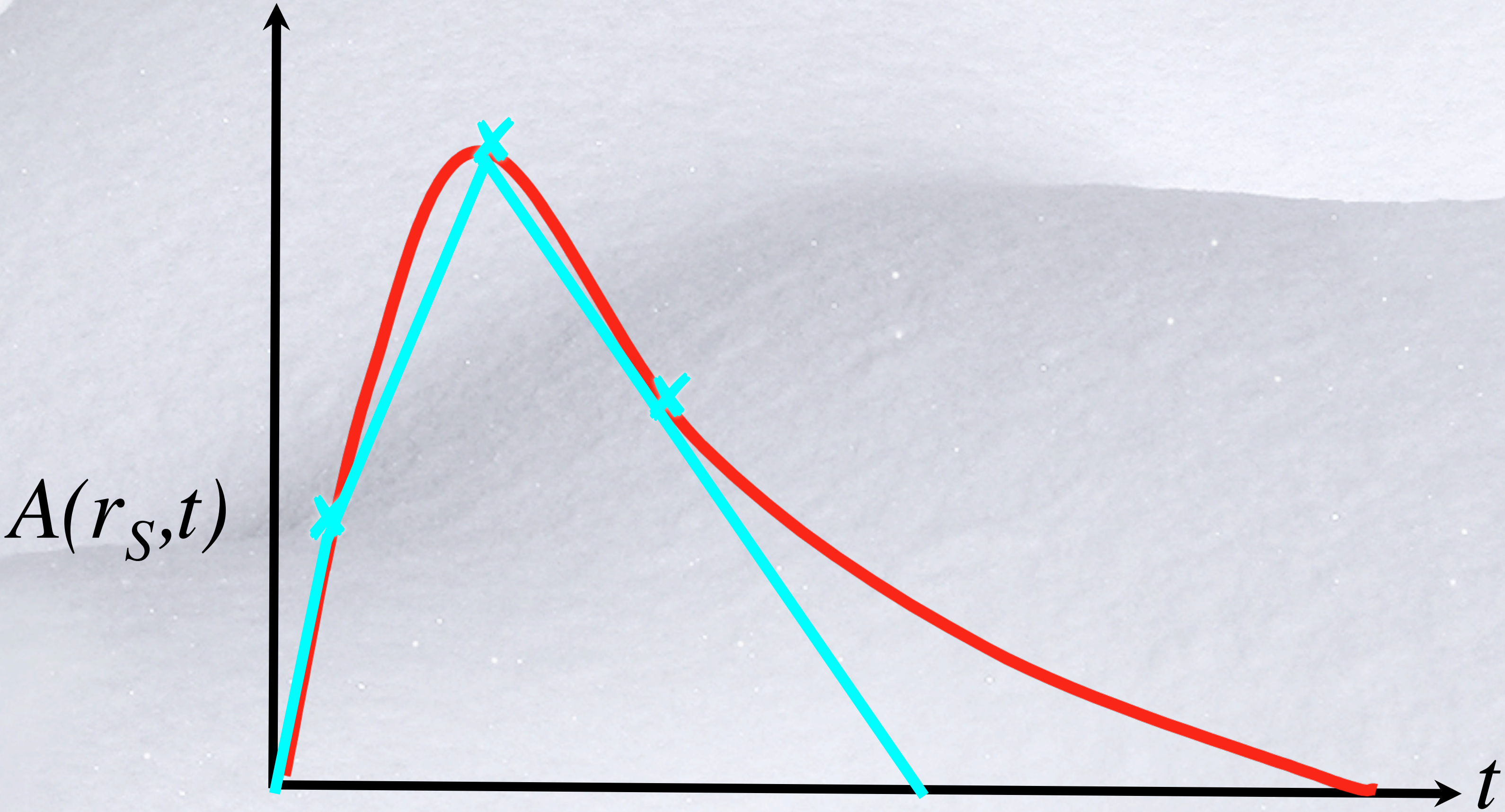
Time-integrated activity

- Importance of sampling...



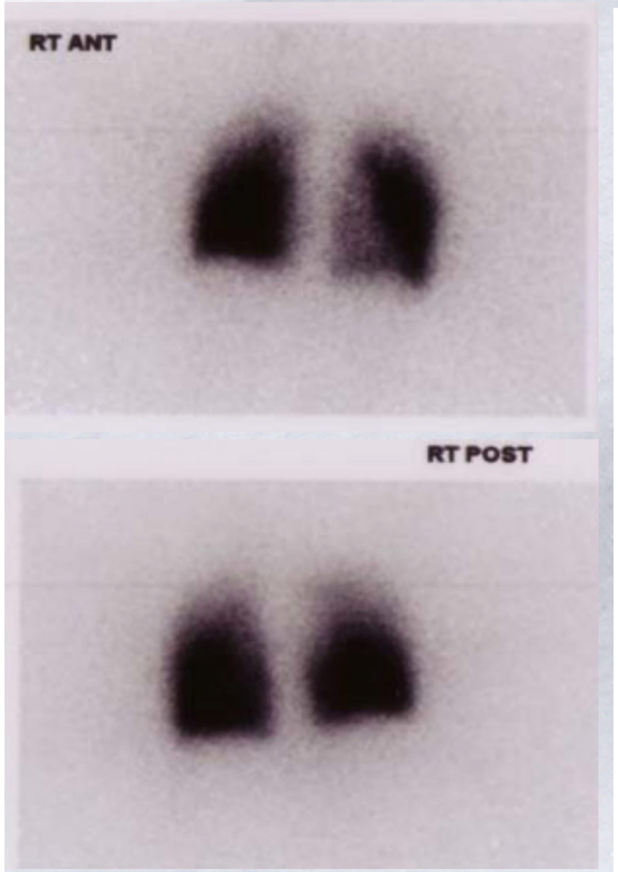
Time-integrated activity

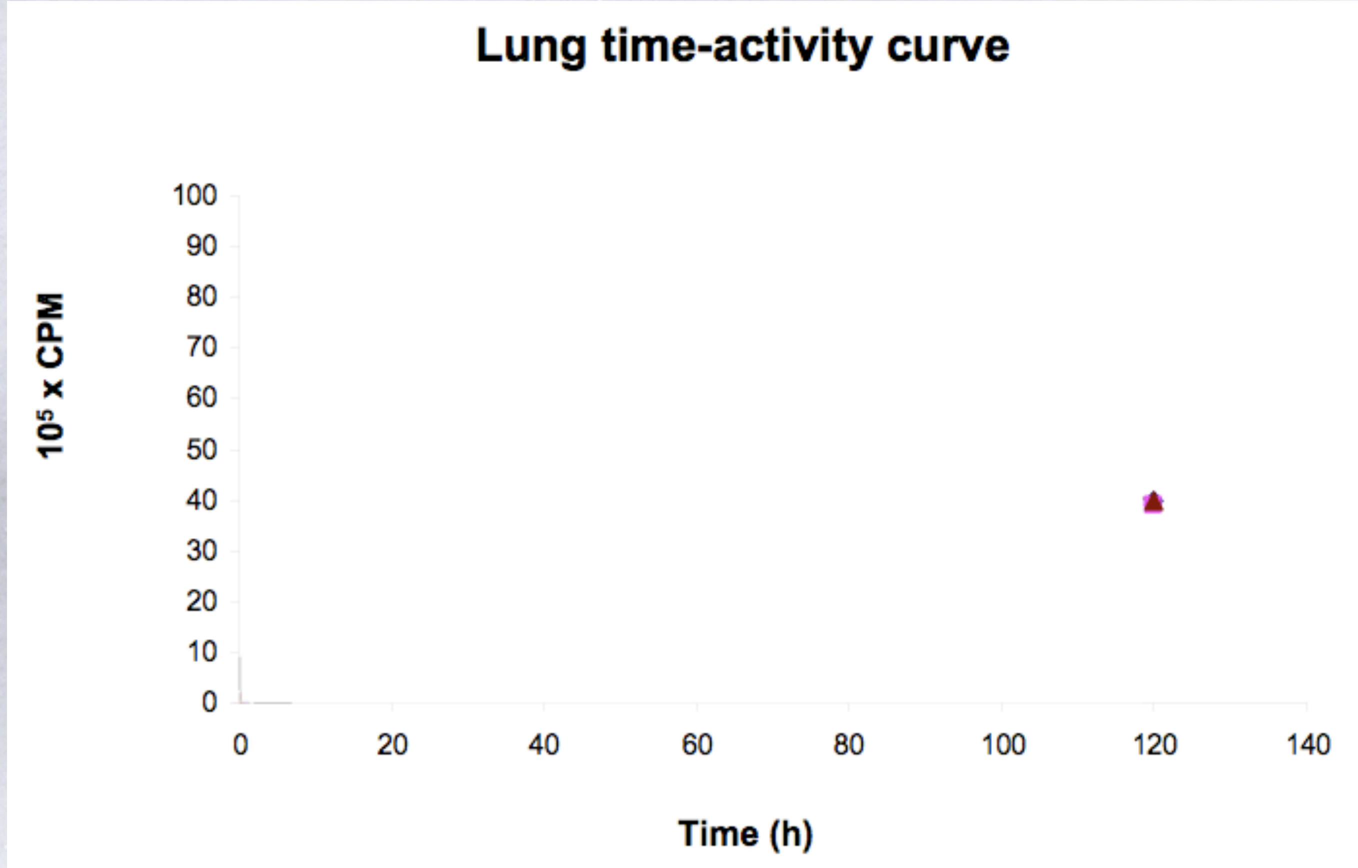
- Importance of sampling...



Time-integrated activity

- Extreme time sampling...





Remember:

$$D(r_T, T_D) = \sum_{r_S} \tilde{A}(r_S, T_D)\, S(r_T \leftarrow r_S)$$

Absorbed dose calculation is a 3 step process:

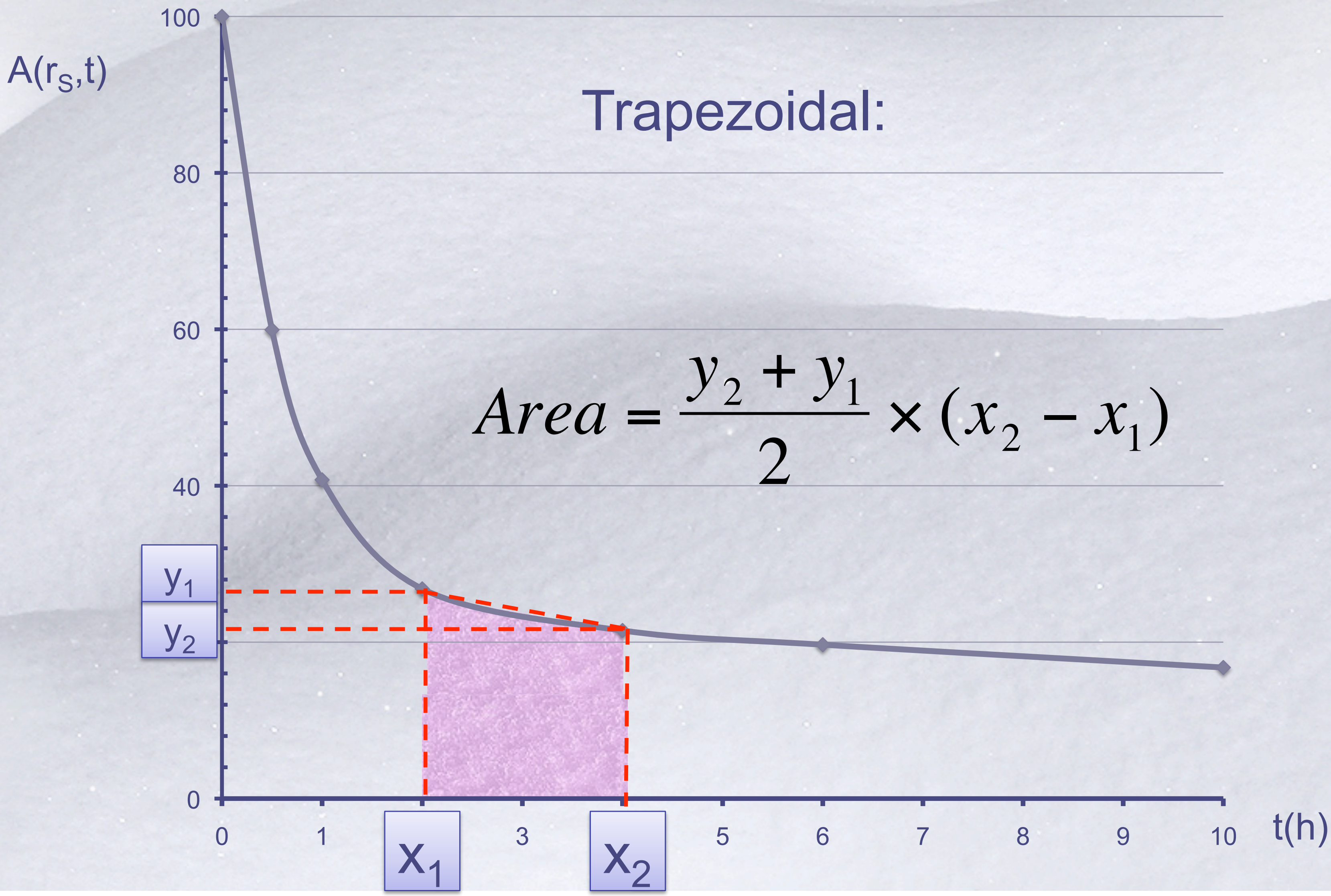
- Quantitative imaging
- Time-integrated activity determination
- S factor calculation

Each step matters for the final result…

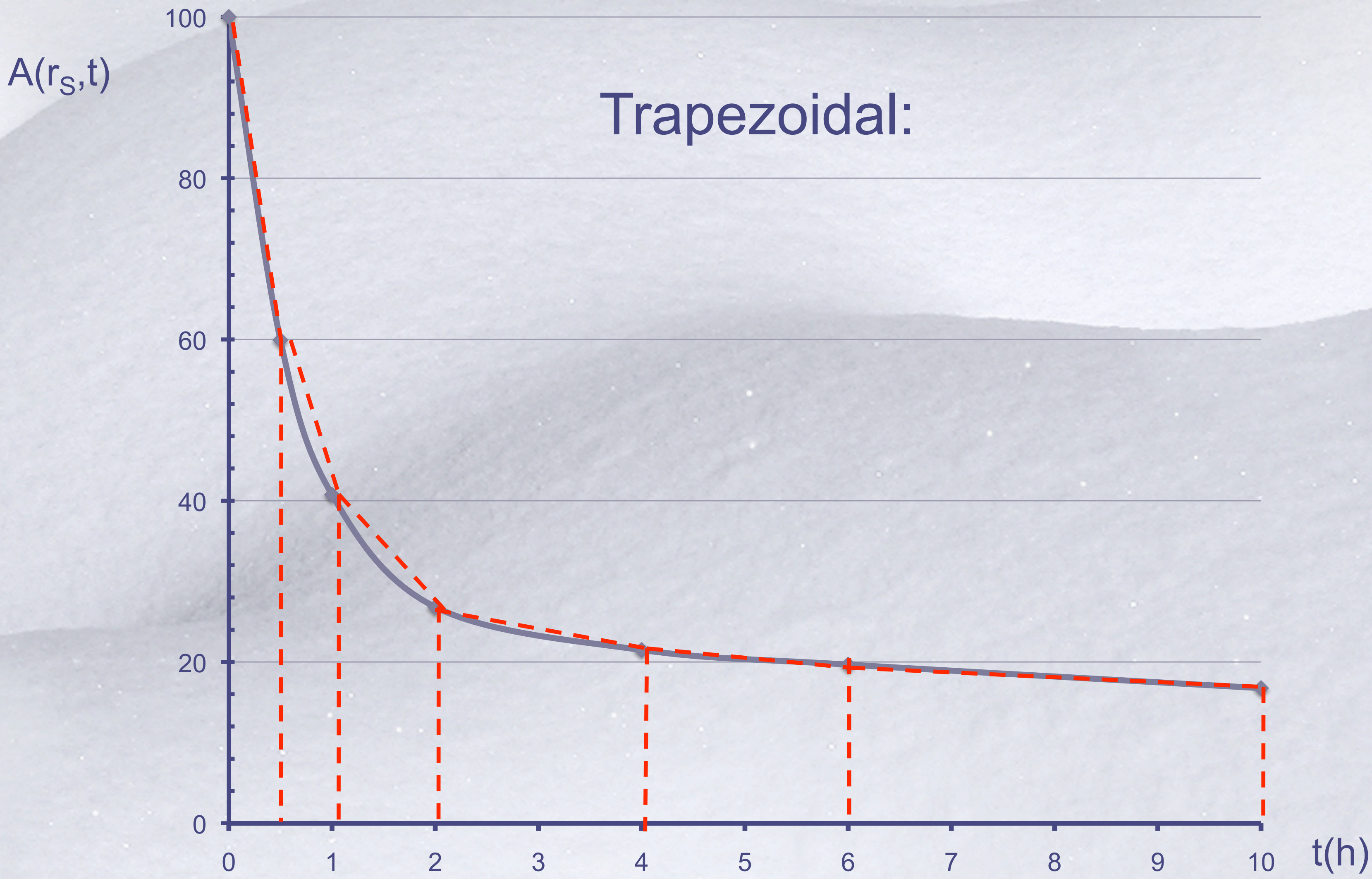
Direct integration

Trapezoidal:

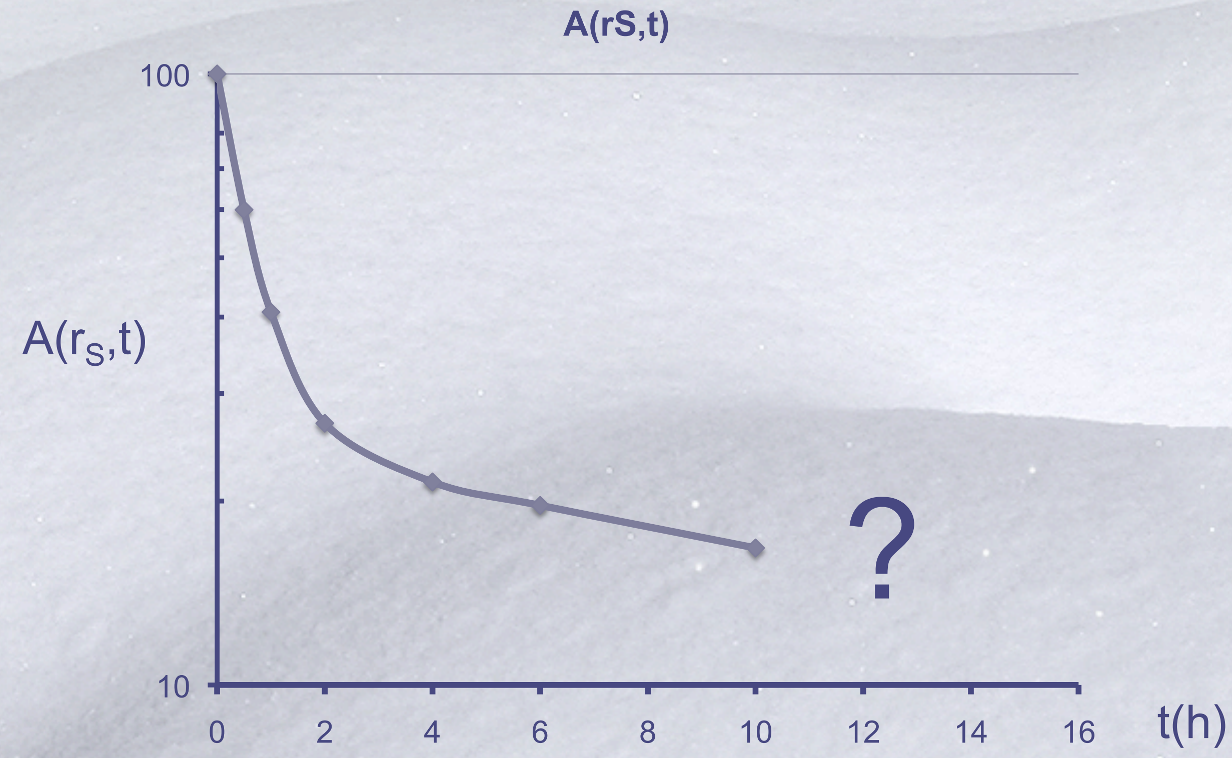
$$Area = \frac{y_2 + y_1}{2} \times (x_2 - x_1)$$



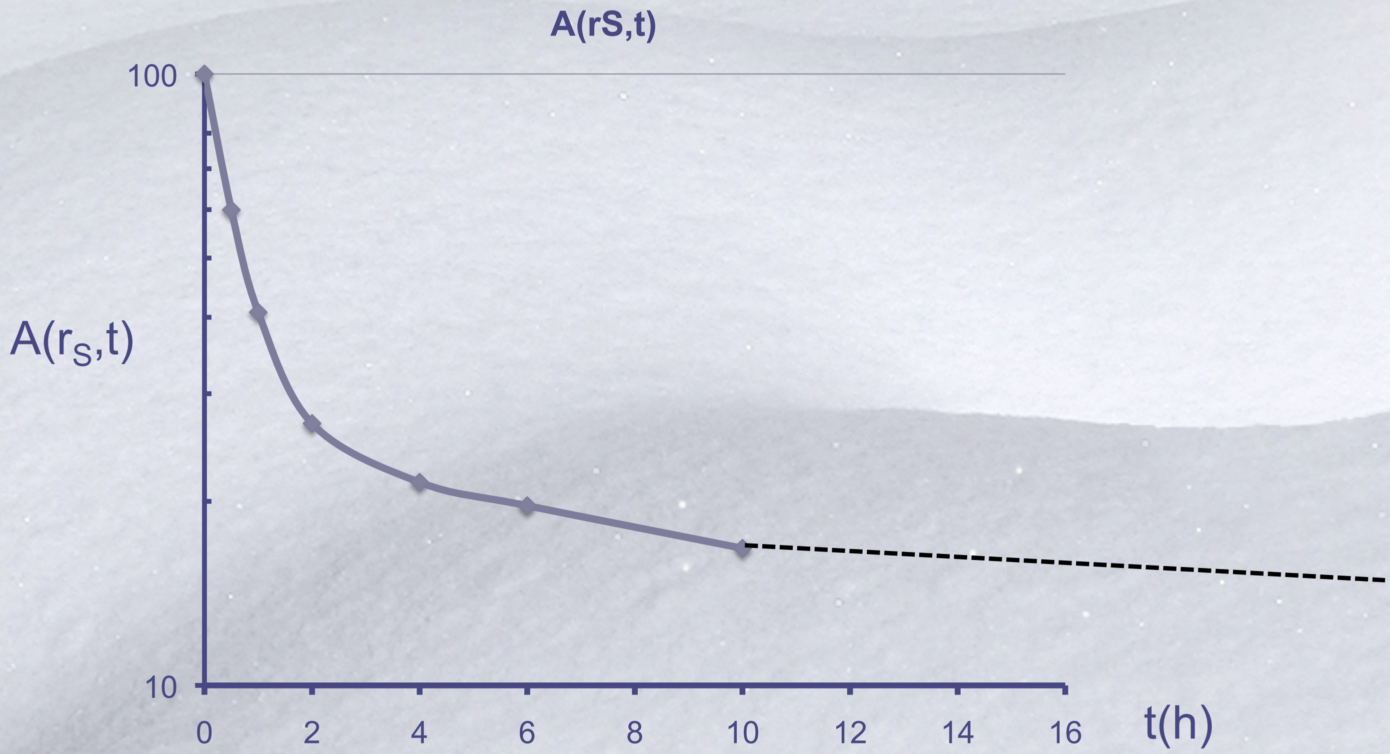
Direct integration



Extrapolation



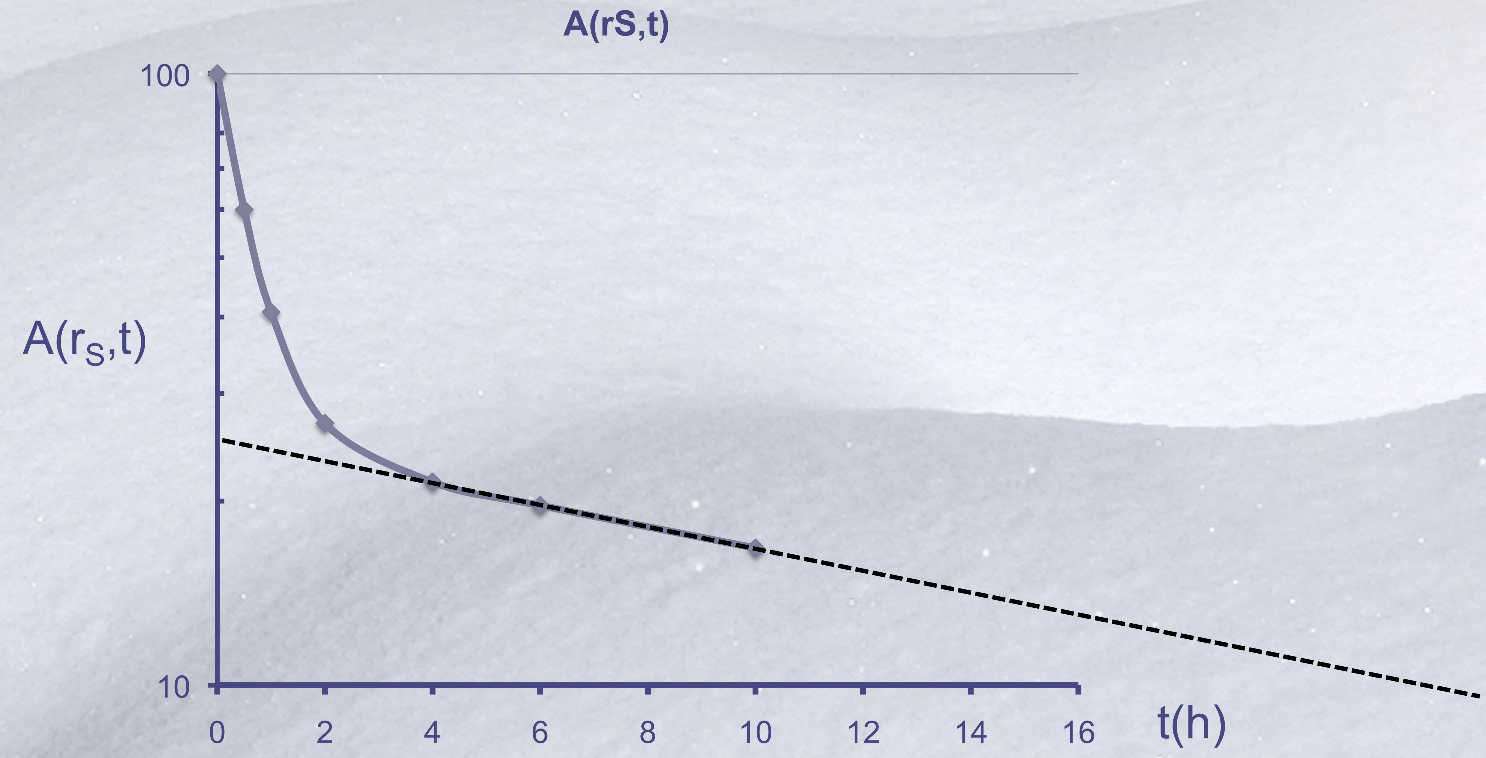
Extrapolation



Use T_{phy} from last experimental time-point

Will OVERESTIMATE $\tilde{A}(r_S, T_D)$

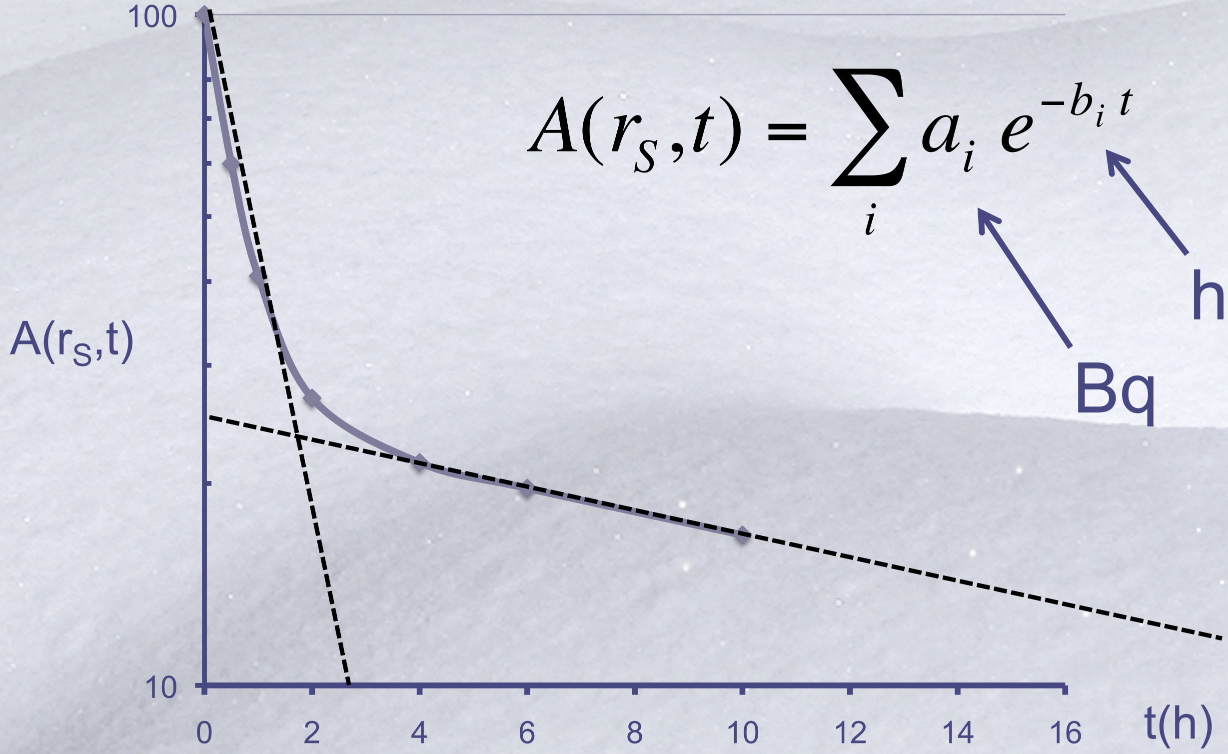
Extrapolation



Exponential fit from last experimental time-points

Probably better

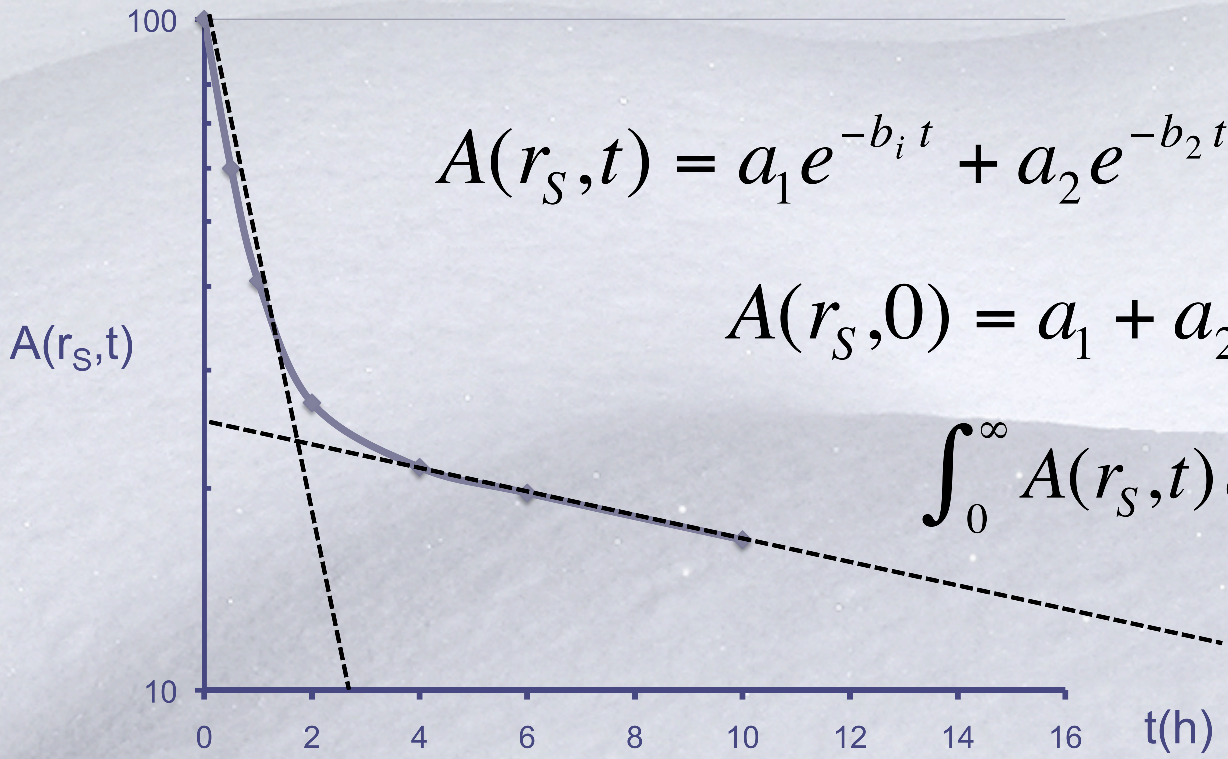
TAC fitting



$$A(r_S,t) = \sum_i a_i\, e^{-b_i\, t}$$

Fit experimental data to a series of exponential components (2 in this example)

TAC fitting



$$A(r_S,t) = a_1 e^{-b_i t} + a_2 e^{-b_2 t}$$

$$A(r_S,0) = a_1 + a_2$$

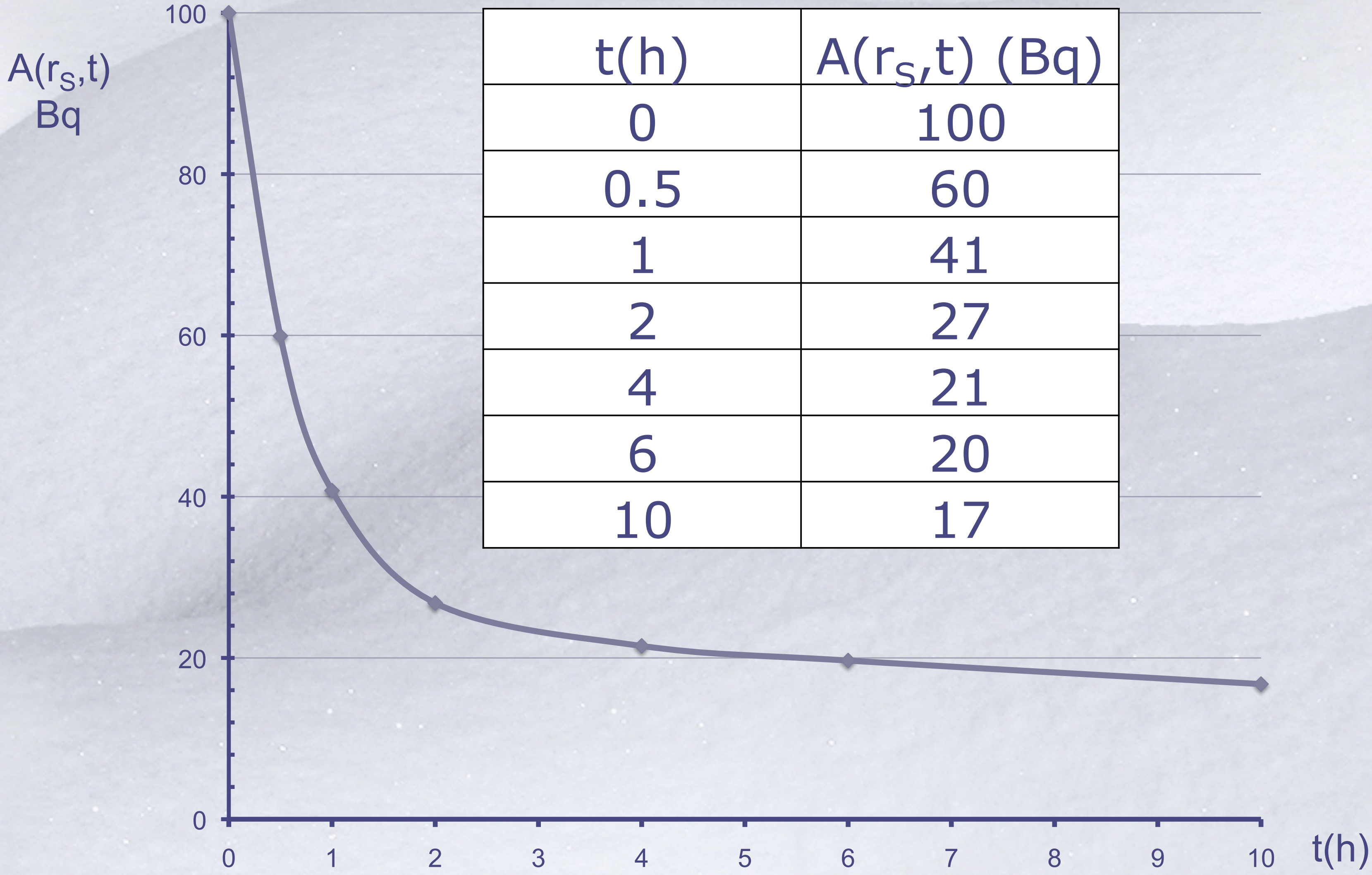
Bq

$$\int_0^\infty A(r_S,t)\,dt = \frac{a_1}{b_1} + \frac{a_2}{b_2}$$

h^{-1}

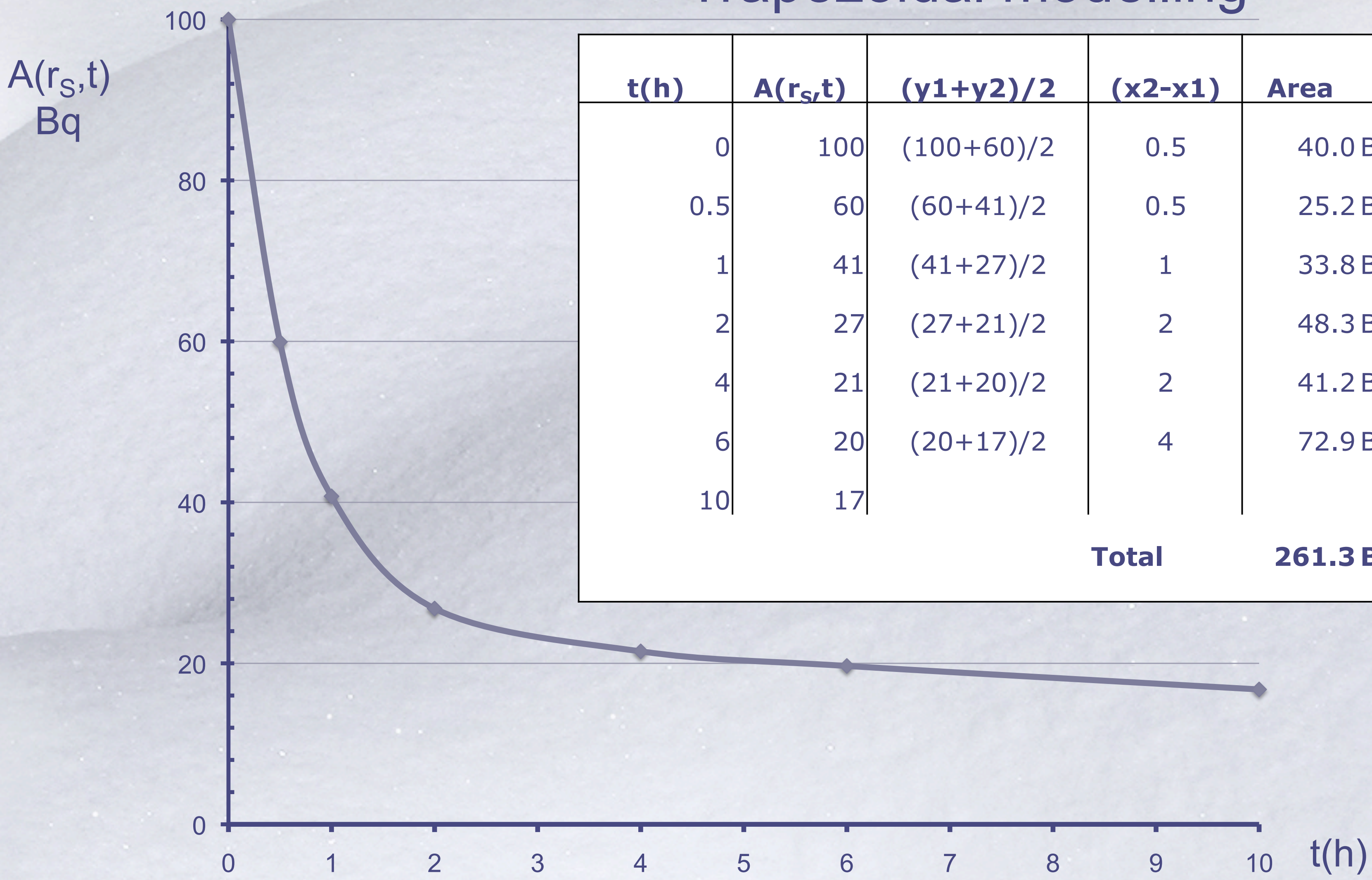
Fit experimental data to 2 exponential components

Numerical example



t(h)	$A(r_S,t)$ (Bq)
0	100
0.5	60
1	41
2	27
4	21
6	20
10	17

Numerical example



Trapezoidal modelling

t(h)	$A(r_S,t)$	(y1+y2)/2	(x2-x1)	Area
0	100	(100+60)/2	0.5	40.0 Bq.h
0.5	60	(60+41)/2	0.5	25.2 Bq.h
1	41	(41+27)/2	1	33.8 Bq.h
2	27	(27+21)/2	2	48.3 Bq.h
4	21	(21+20)/2	2	41.2 Bq.h
6	20	(20+17)/2	4	72.9 Bq.h
10	17			
			Total	**261.3 Bq.h**

Numerical example

Extrapolation from 10h to infinity:

Using the "slow decay" constant (0.04 h^{-1})

$$\tilde{A}(r_S, 10h \to \infty) = 1.443 \times A(10h) \times T_{Eff}$$

$$= \frac{1}{\ln 2} \times A_0 \times \frac{\ln 2}{\lambda_{Eff}} = \frac{A(10h)}{\lambda_{Eff}}$$

$$= \frac{17}{0.04} = 425 Bq.h$$

$$\tilde{A}(r_S, \infty) = 261.3 + 425 = 686.3 Bq.h$$

Numerical example

Extrapolation from 10h to infinity:

Using the physical decay constant (i.e. h^{-1} for ^{131}I)

$$\tilde{A}\left(r_S, 10h \rightarrow \infty\right) = 1.443 \times A(10h) \times T_{Phy}$$

$$= 1.443 \times 17 \times 8.04 \times 24$$

$$= 4733.5 Bq.h$$

This highlights how extrapolating with the physical decay constant can be REALLY wrong…

Numerical example

A bi-exponential fit yields:

$$A(r_S,t) = 25e^{-0.04\,t} + 75e^{-1.5\,t}$$

With:

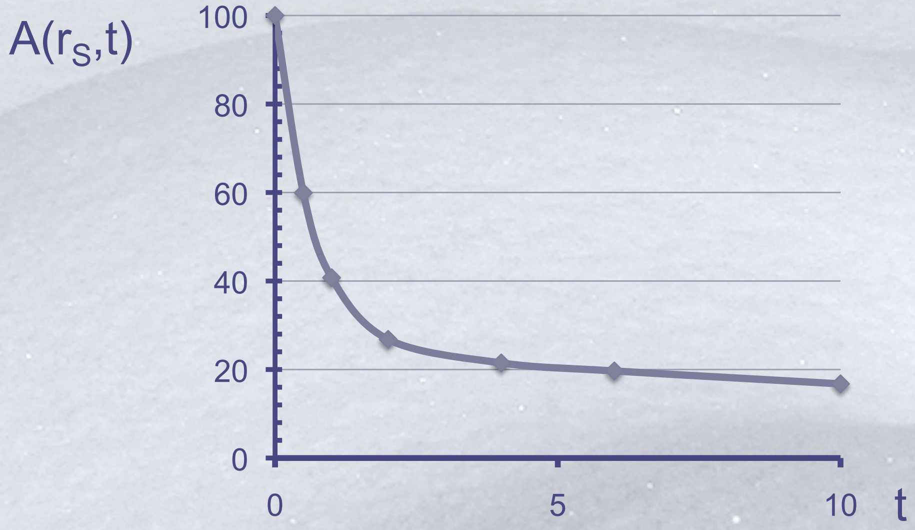
$$T_1 = \frac{Ln2}{0.04} = 17.3h$$

$$T_2 = \frac{Ln2}{1.5} = 0.46h$$

$$\int_0^\infty A(r_S,t)\,dt = \frac{25}{0.04} + \frac{75}{1.5} = 675\,Bq.h$$

And 675 ~ 686.3 Bq.h…

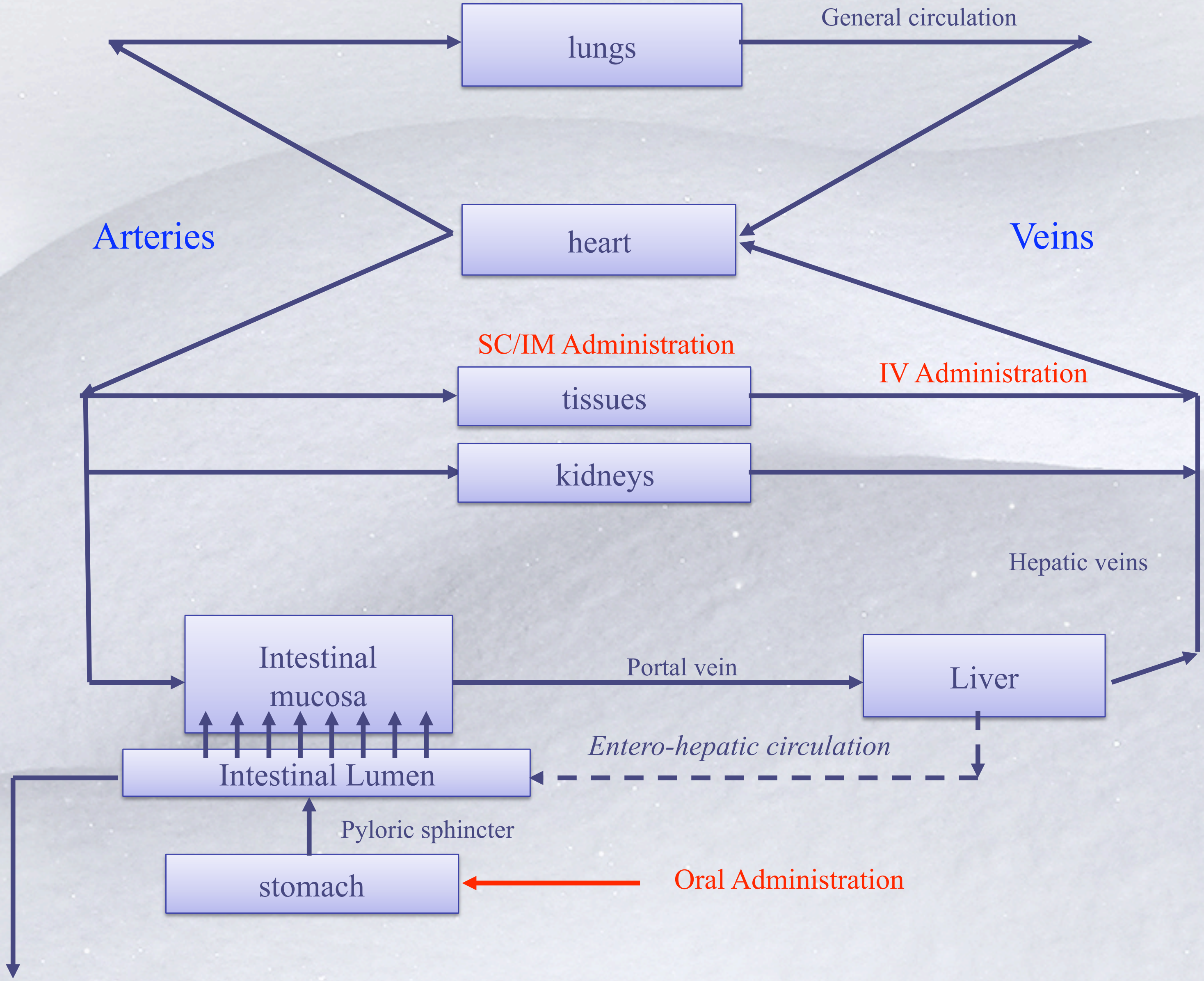
TAC fitting



In the previous example:
$A(r_S,t)$ « looks » bi-exponential.
Is there a relevance in trying to fit experimental data with exponentials?

Introduction to *compartmental analysis*

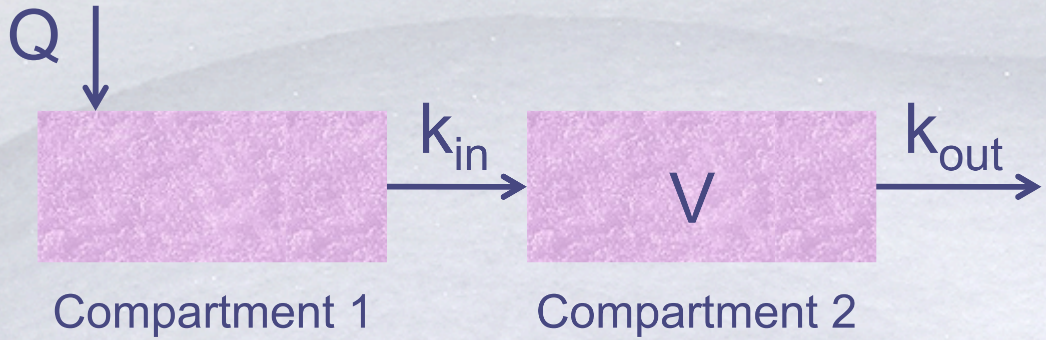
ADME:
Absorption, Distribution, Metabolism, Excretion



Compartmental analysis

- A system is described as a group of compartments
  - Opened or closed
  - One, 2, many compartments
  - Topology: catenary, mammillary
- The behaviour of the substance of interest in each compartment is unique (homogeneous).
- A compartment has a volume that may or may not be relevant from a physiology point of view…
- Compartments are linked through transfer rate coefficients

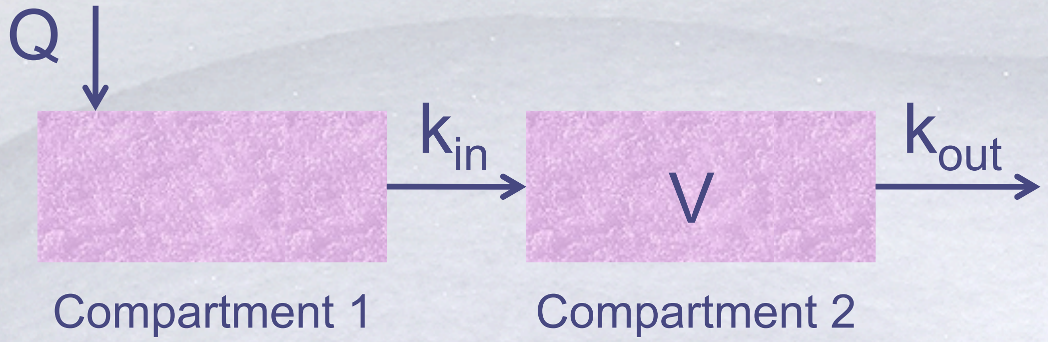
Example: 2 compartments, open model



- Bolus injection (IV) of Q (mg) of drug
- Transfer from compartment 1 to 2 with k_{in} (s^{-1})
- Input rate in compartment 2: e(t)

$$e(t) = Q \times k_{in} \times e^{-k_{in} t}$$

Example: 2 compartments, open model



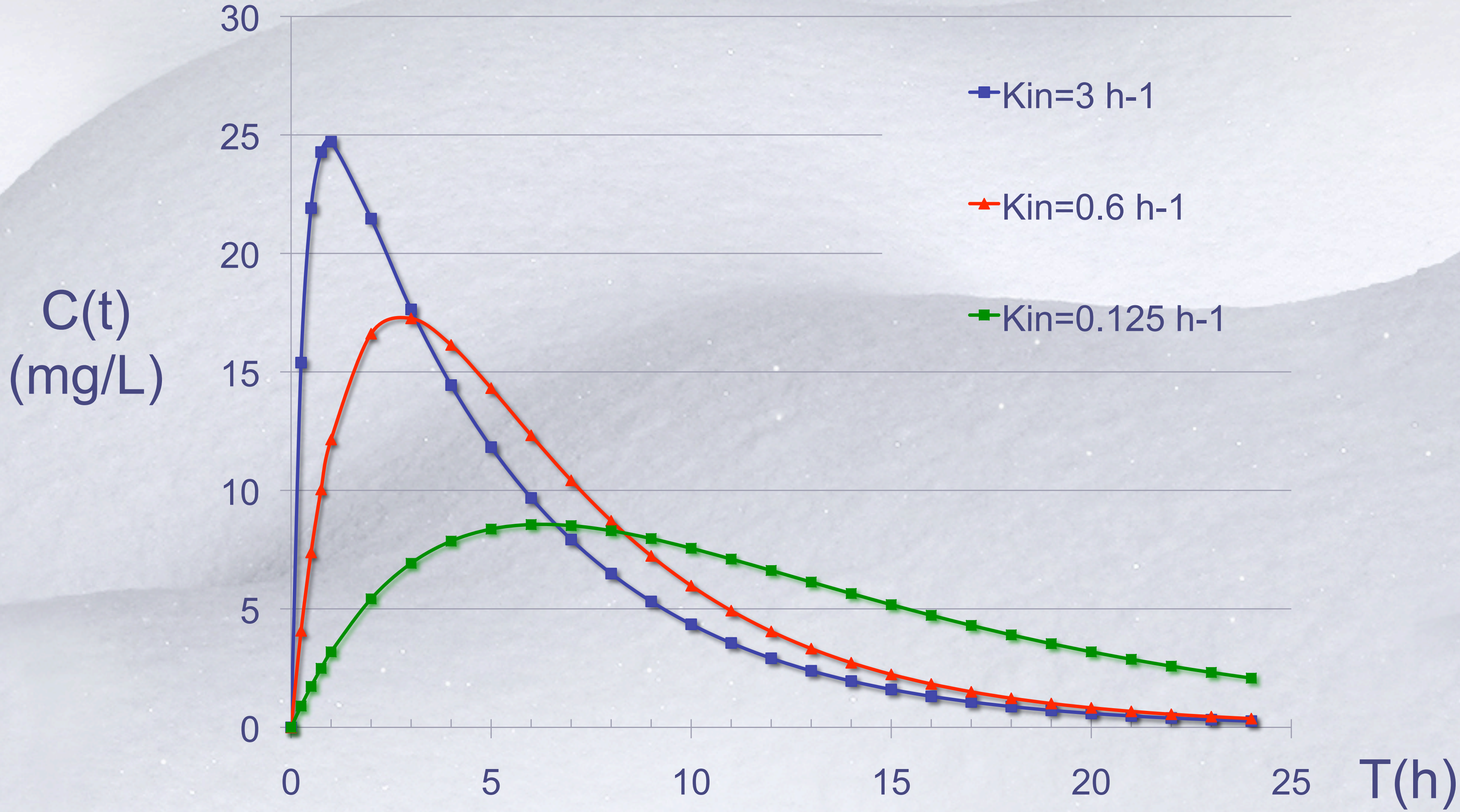
$$C(t) = \frac{Q}{V} \times \frac{k_{in}}{k_{in} - k_{out}} \times \left(e^{-k_{out}t} - e^{-k_{in}t} \right)$$

C(t): concentration in compartment 2 at time t:

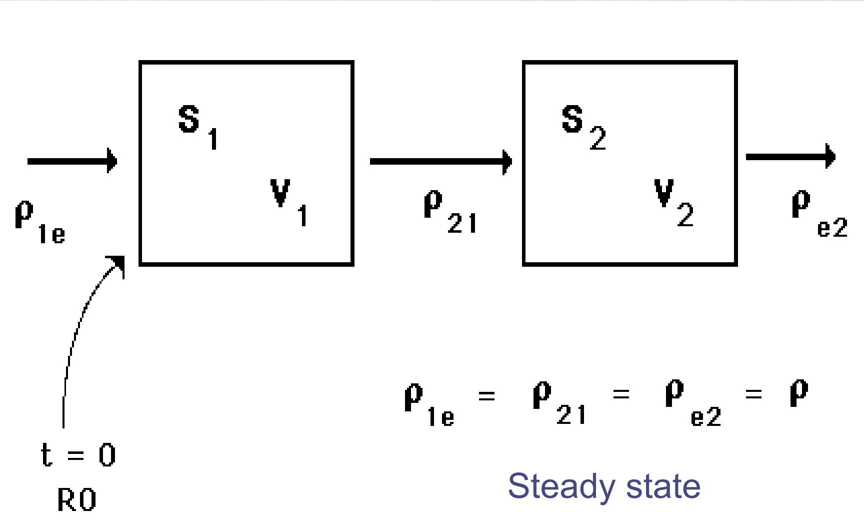
C(t) in mg/L

Numerical application:

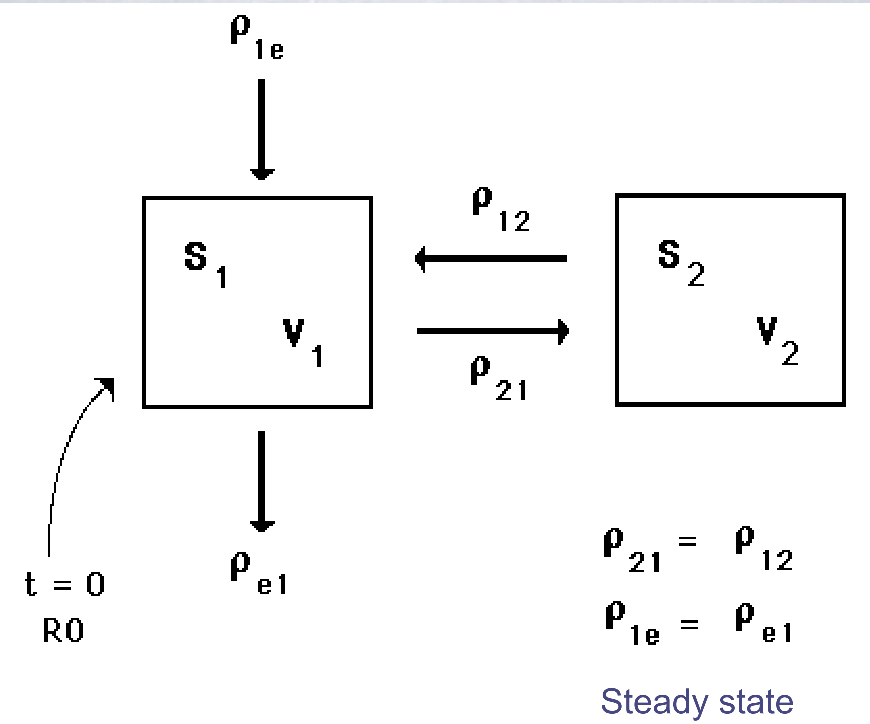
Influence of k_{in}: Q= 600 mg; k_{out} = 0.2 h^{-1}; V=20L



Other examples



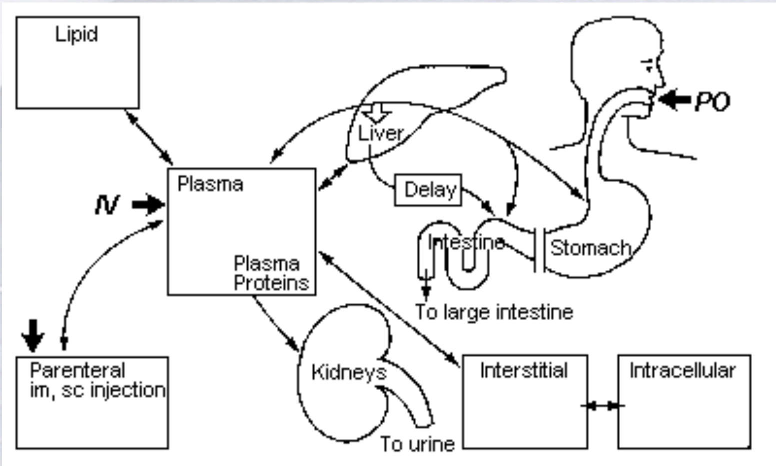
Catenary:
Exchange with outside world through the 2 compartments

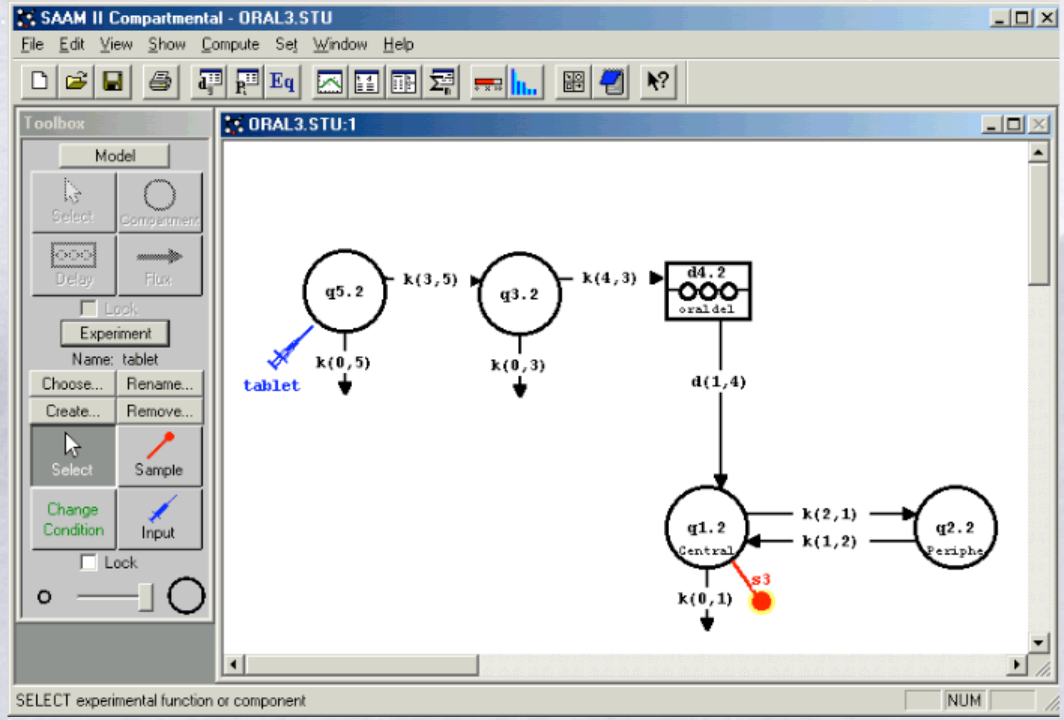


Mammillary:
Exchange with outside world through one compartment only (central compartment)

Softwares

- Many possibilities...





- Check bibliography...
- TEST the software!

References & Acknowledgements

- EANM Dosimetry Committee
- MG Stabin "Fundamentals of Nuclear Medicine Dosimetry"
- MIRD Pamphlet 21. Bolch et al. JNM 2009; 50:477-484