parametric imaging of glucose metabolism in biological tissues

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credits

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...and to

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- fondazione CARIGE
- paramed srl

glucose and FDG

glucose metabolism

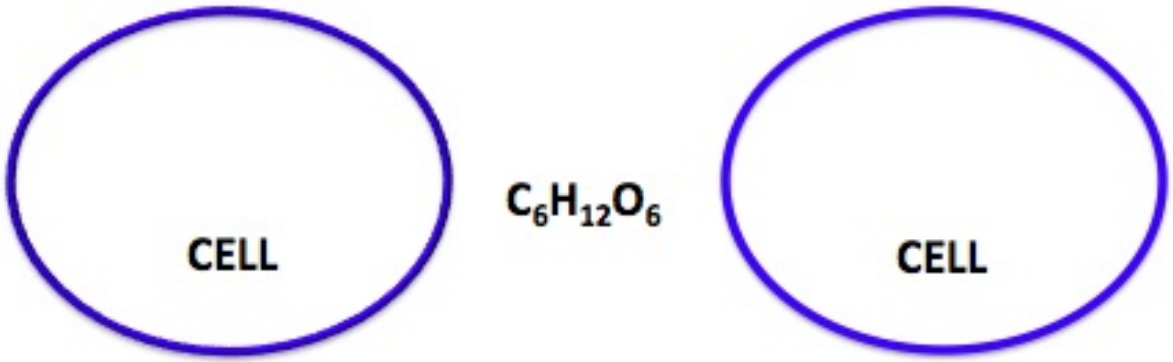
- energy is required for the normal functioning of the organs in a living organism
- glucose provides most of the energy necessary to the body

glucose metabolism is the cornerstone of life

a two-way destiny

a two-way destiny

first destiny



a two-way destiny

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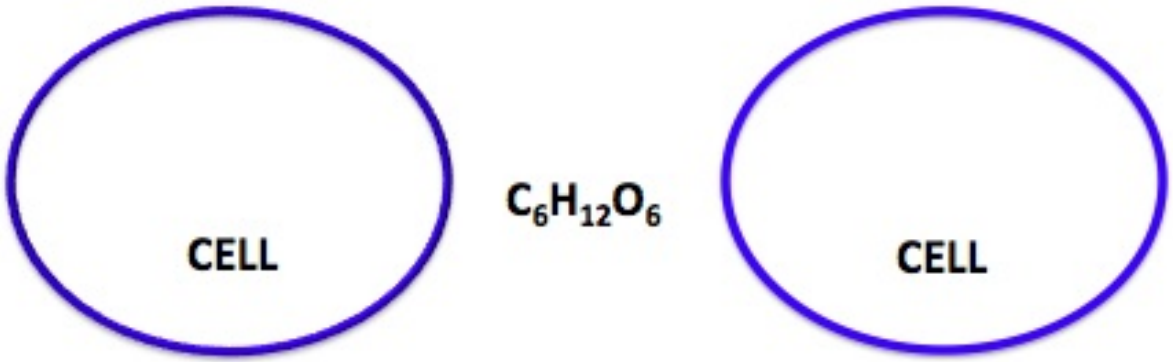
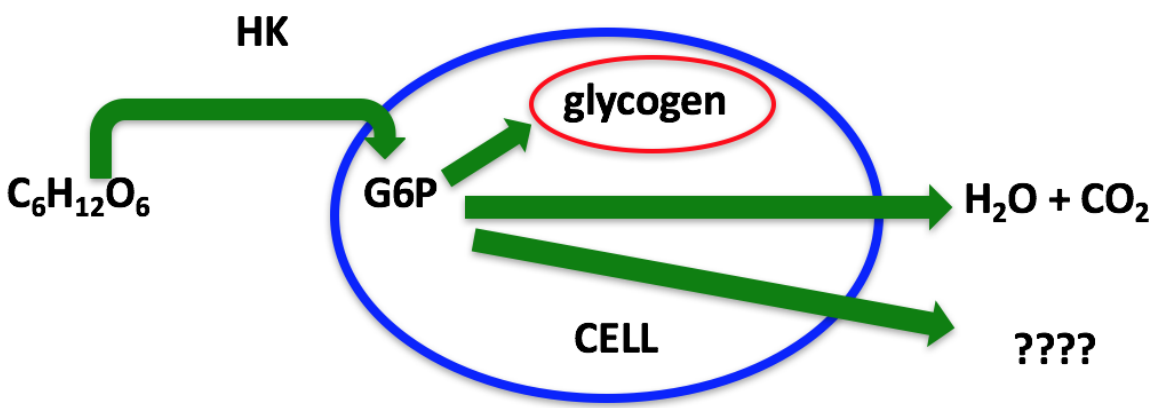


second destiny



pathologies

diabetes

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- braunstein 1921: glucose secretion in the urine disappears in those who develop cancer
- warburg 1924: cancer cells increase glucose uptake in aerobic conditions
- glucose cell metabolism: it's all about cancer (ward and thompson, *cancer cells*, 2012)

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therefore: **imaging glucose metabolism would help diagnosis, prognosis and therapy**

glucose-PET

positron emission tomography (PET) is a functional medical imaging modality

in principle, PET could image glucose metabolism by means of a procedure like this:

1. glucose ($C_6H_{12}O_6$) is tagged by means of a positron emitter
2. the tagged glucose tracer is injected into the blood
3. each emitted positron annihilates with a tissue electron, emitting light along a perfect straight line
4. collimators collect the emitted light whose distribution is a signature of glucose distribution in time and space

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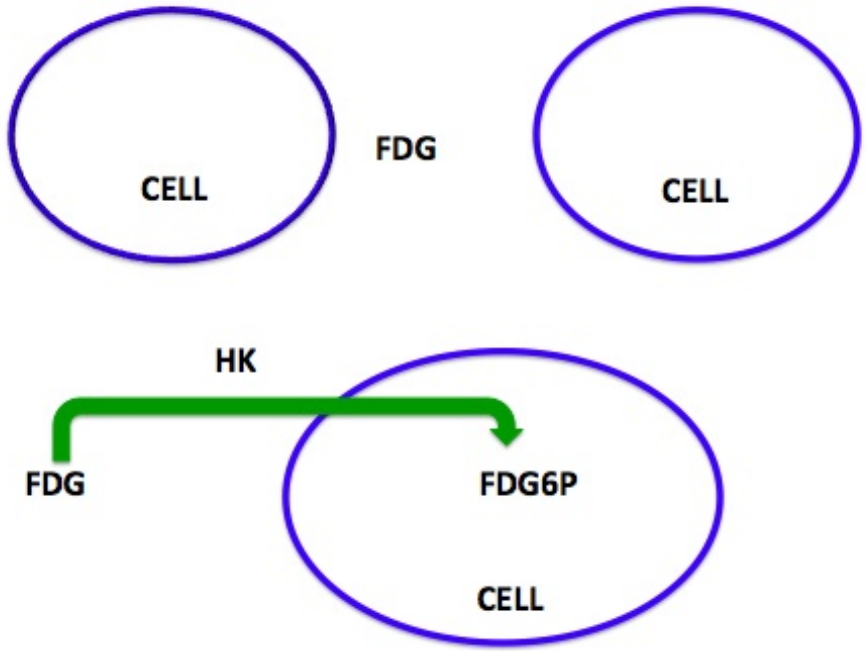
warning: this can't work:

- ^{15}O decays in 120 seconds
- tritium decays in 2000 years (and is a weak beta emitter)
- ^{11}C decays in 20 minutes (but asks for very complex dynamic analysis)

FDG-PET

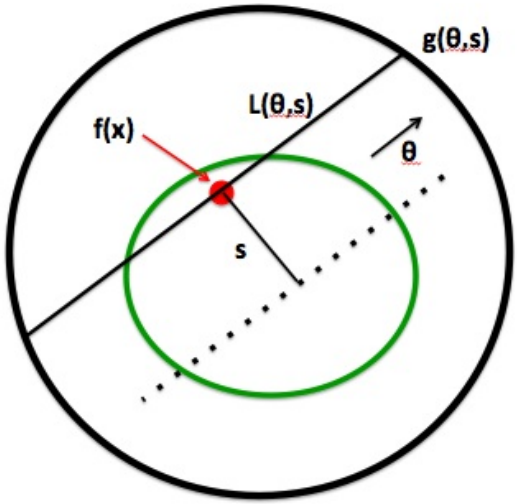
fluorodeoxyglucose (FDG) is a glucose analog



FDG decays in 2 hours: FDG-PET is feasible

mathematical model

FDG-PET sinograms



- $f(x)$: tracer distribution
- $L(\theta, s)$: light path with orientation θ at distance s from the origin
- $g(s, \theta) = \int_{L(\theta,s)} f(x)dx$

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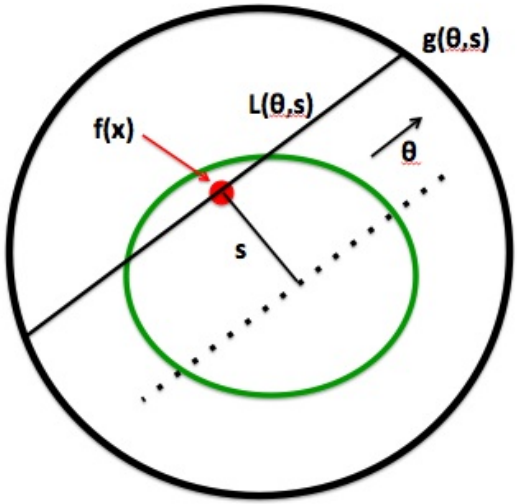

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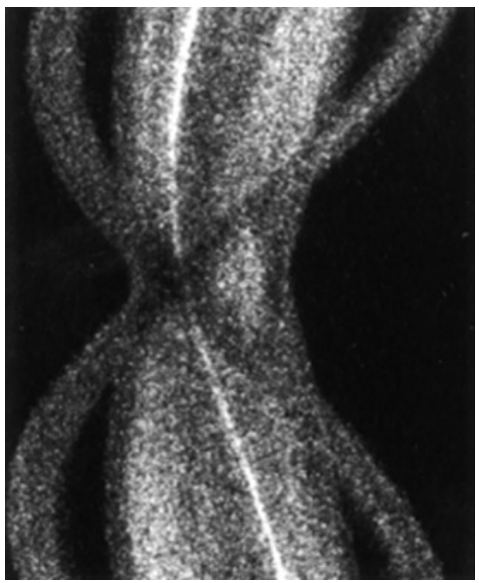

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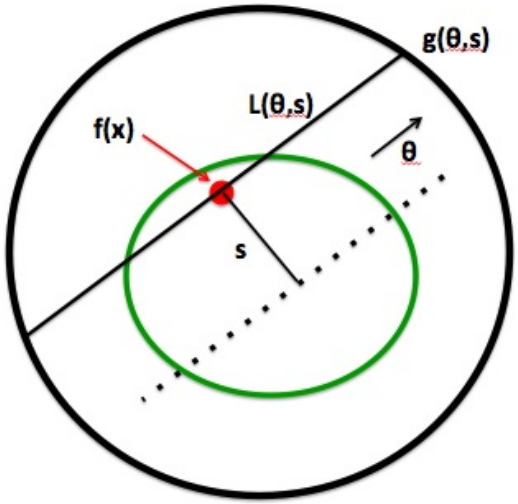

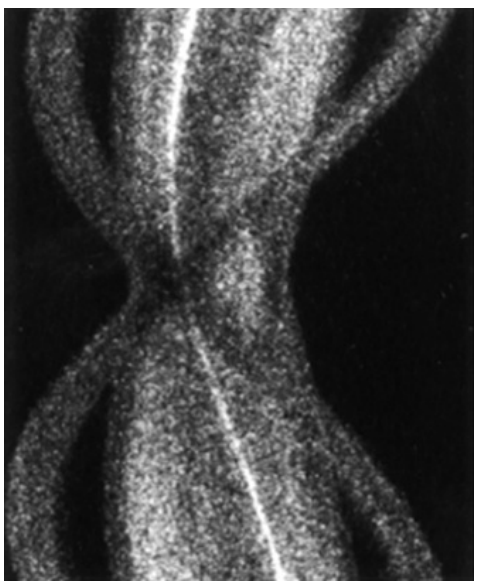

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$$g = Rf$$

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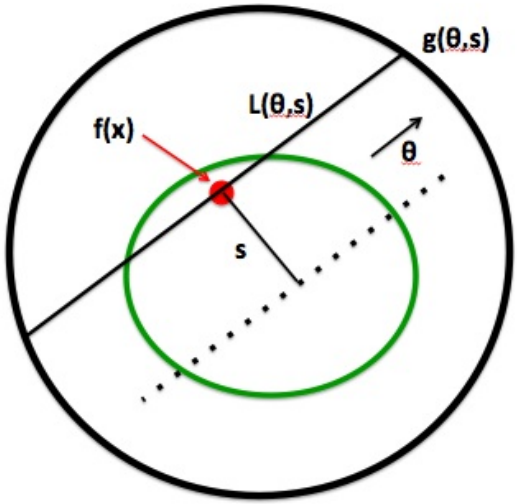

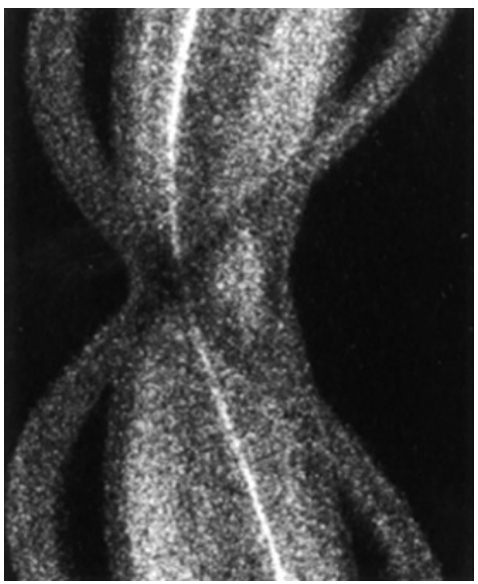

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note that:

- the radon transform is compact in (weighted) L^2-spaces
- **therefore** the inverse radon transform is not bounded
- **therefore** naive solution are numerically unstable
- **therefore,** at some stage, **regularization** is needed

image reconstruction: maximum likelihood

the inverse problem of FDG-PET image reconstruction:
given the FDG-PET sinogram reconstruct the FDG distribution in the whole body

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bayes theorem + MAP:

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$$f_{est} = \arg\max_{f \geq 0} \pi(f|g)$$

example of $\pi_{prior}(f)$: $f \geq 0$

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poisson noise: kullbach-leibler

$$L(f,g) = \sum_i g_i \log \frac{g_i}{(Rf)_i} + (Rf)_i - g_i$$

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EM: $f^{(k+1)} = \frac{f^{(k)}}{R^T 1} R^T \frac{g}{Rf^{(k)}}$

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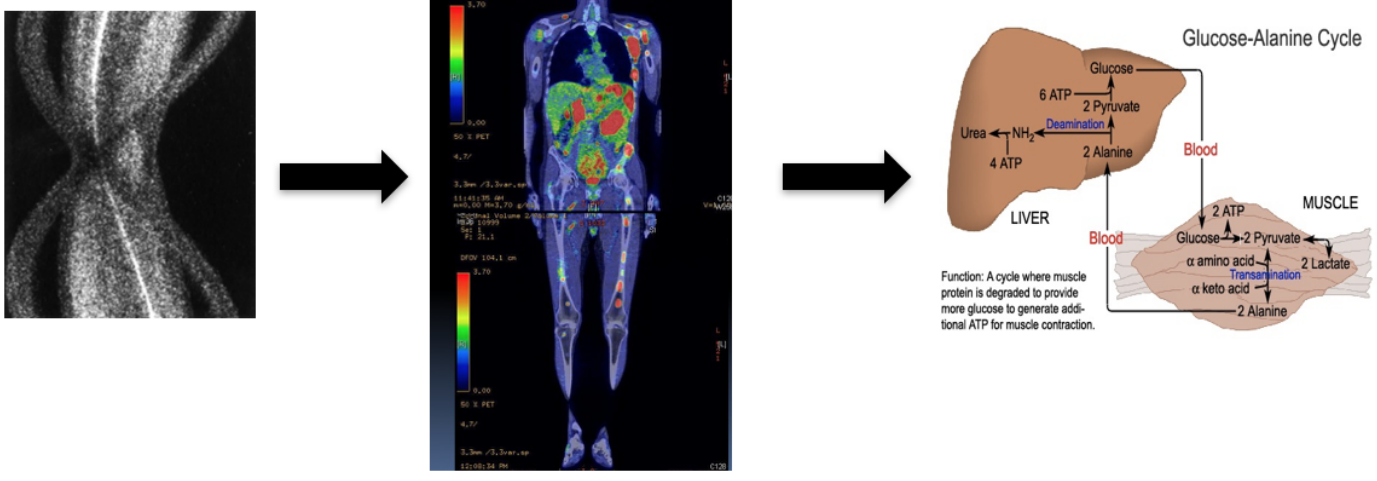
issues:

- how to regularize: choose the right stopping rule (benvenuto and piana, *inverse problems*, 2014)
- how to go fast : gradient projection approaches (benvenuto, zanella, zanni and bertero, *inverse problems*, 2010)
- how to encode more sophisticated information in $\pi_{prior}(f)$ (calvini, massone, nobili and rodriguez, IEEE *transactions on nuclear science*, 2006; sorrentino et al, *annals of applied statistics*, 2013)

compartments

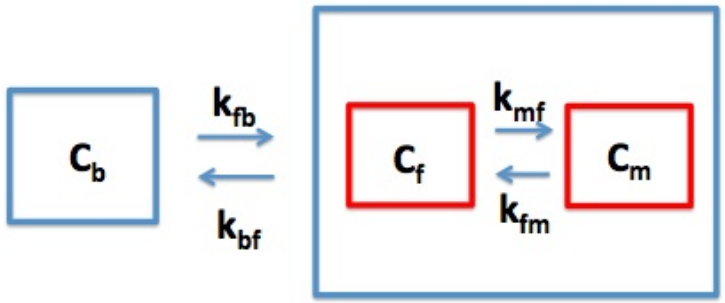
from body to tissue



- image reconstruction provides information on FDG metabolism at a whole body level using static data
- in order to have information on tissue metabolism one needs
  - dynamic data
  - compartmental analysis

two-compartment model

(sokoloff et al, *j neurochem*, 1977)



- compartment b: tracer input
- compartments f and m: free (out of cells) and metabolized FDG
- C_b: input tracer concentration
- C_f and C_m: concentration of free and metabolized FDG
- $k_{fb}, k_{bf}, k_{mf}, k_{fm}$: tracer coefficients (minutes^{-1}): measure the efficiency with which tracer passes from one functional compartment to the other

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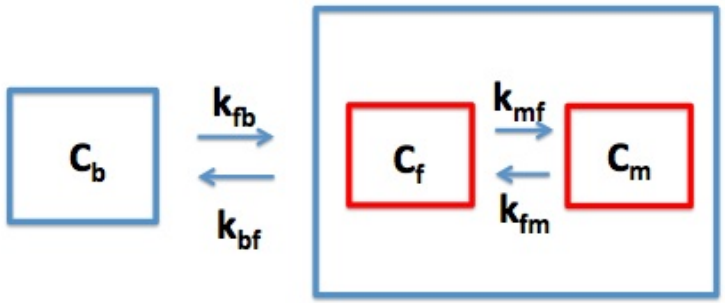

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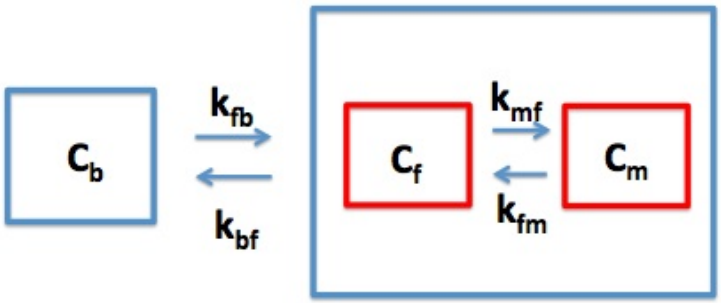
physical assumptions:

- tracer is uniformly distributed in each compartment
- diffusive effects are neglected
- physiological processes are in a steady state
- conservation of tracer between compartments holds

forward problem



$$\dot{C}_f = -(k_{bf} + k_{mf})C_f + k_{fm}C_m + k_{fb}C_b$$

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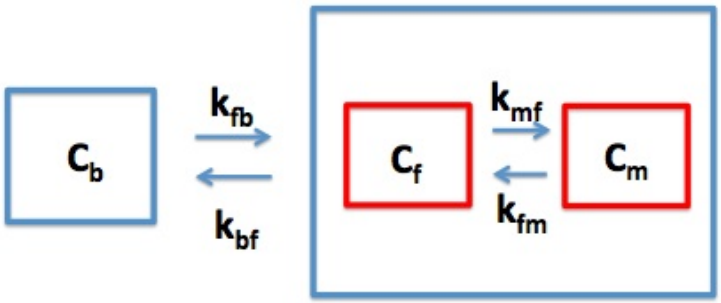

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$$M = \begin{pmatrix} -(k_{bf} + k_{mf}) & k_{fm} \\ k_{mf} & -k_{fm} \end{pmatrix} \qquad W(t) = \begin{pmatrix} C_b(t) \\ 0 \end{pmatrix} \qquad C = \begin{pmatrix} C_f \\ C_m \end{pmatrix}$$

$$\dot{C} = MC + k_{fb}W$$

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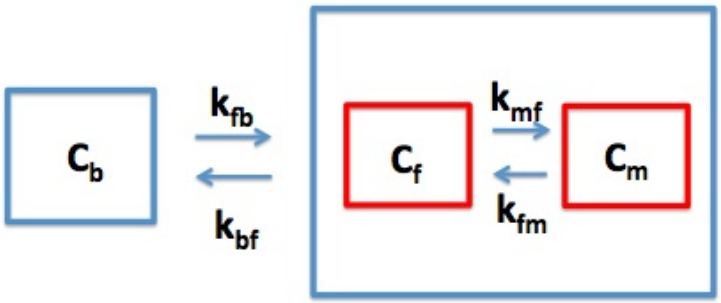

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$$\dot{C} = MC + k_{fb}W$$

$$C(t) = k_{fb} \int_0^t C_b(u) \exp((t-u)M) e_1 \, du$$

inverse problem

- the measured data are C_b and $C_f + C_m$

inverse problem

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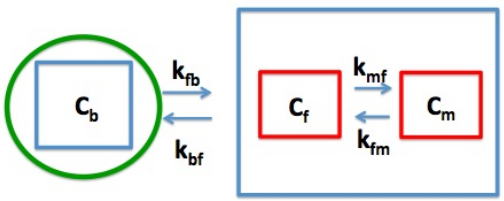
- C_b is obtained from Region of Interests drawn over PET images of the left ventricle at many times t



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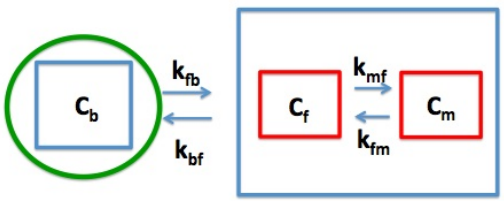
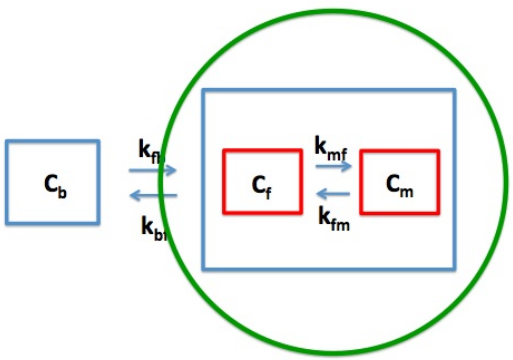


- $C_f + C_m$ is obtained from Region of Interests drawn over PET images of the overall organ at many times t



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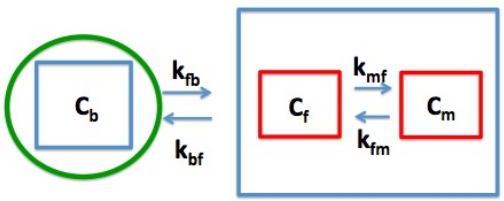

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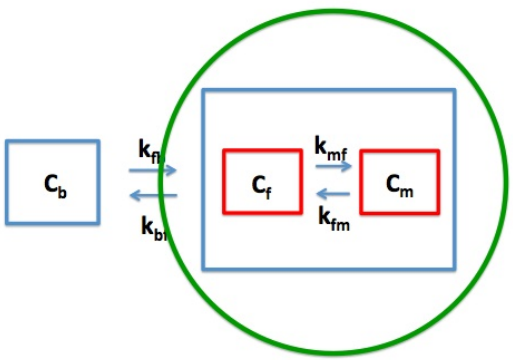

- the inverse problem to solve is

$$C_f + C_m = \alpha^T k_{fb} \int_0^t C_b(u) \exp((t-u)M) e_1 \, du \qquad \alpha = \begin{pmatrix} 1 \\ 1 \end{pmatrix}$$

uniqueness

(delbary, garbarino and vivaldi, *inverse problems*, 2016)

theorem: given $\mathbf{k}$ and $\mathbf{k}'$ solutions of the equation

$$C_f + C_m = \alpha^T k_{fb} \int_0^t C_b(u) \exp((t-u)M) e_1 \, du \qquad \alpha = \begin{pmatrix} 1 \\ 1 \end{pmatrix}$$

such that $\mathbf{k}, \mathbf{k}' \in \mathbb{R}^4_+ \setminus \{\mathbf{0}\}$, then $\mathbf{k} = \mathbf{k}'$.

Proof (sketch): computing the laplace transform of the equation leads to

$$\alpha^T (s - M')^{-1} e_1 = \alpha^T (s - M)^{-1} e_1 .$$

this implies

$$\frac{Q(s)}{P(s)} = \frac{Q'(s)}{P'(s)}$$

where $Q(s), P(s)$ are co-prime polynomials of degree 1 and 2, respectively. this implies $Q(s) = Q'(s)$ and $P(s) = P'(s)$. this in turn implies $\mathbf{k} = \mathbf{k}'$

inversion method

given $\mathbf{k} = (k_{fb}, k_{bf}, k_{mf}, k_{fm}) \in \mathbb{R}^4_+$ and C_b measured from PET images, define

$$\mathcal{F} : \mathbb{R}^4_+ \to C^1(\mathbb{R}_+) \qquad [\mathcal{F}(\mathbf{k})](t) = \alpha^T k_{fb} \int_0^t C_b(u) \exp((t-u)M) e_1 \, du$$

and find $\mathbf{k}$ such that

$$\mathcal{F}(\mathbf{k}) = C_f + C_m$$

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newton's algorithm:

$$F(\mathbf{k}) := (C_f + C_m) - \mathcal{F}(\mathbf{k})$$

$$F(\mathbf{k}) = 0$$

$$\text{initial guess:} \qquad \mathbf{k} = \mathbf{k}_0 + \mathbf{h}$$

$$F'(\mathbf{k}_0)\mathbf{h} = -F(\mathbf{k}_0) \qquad \text{(regularization needed)}$$

$$\text{update:} \qquad \mathbf{k}_0 = \mathbf{k}$$

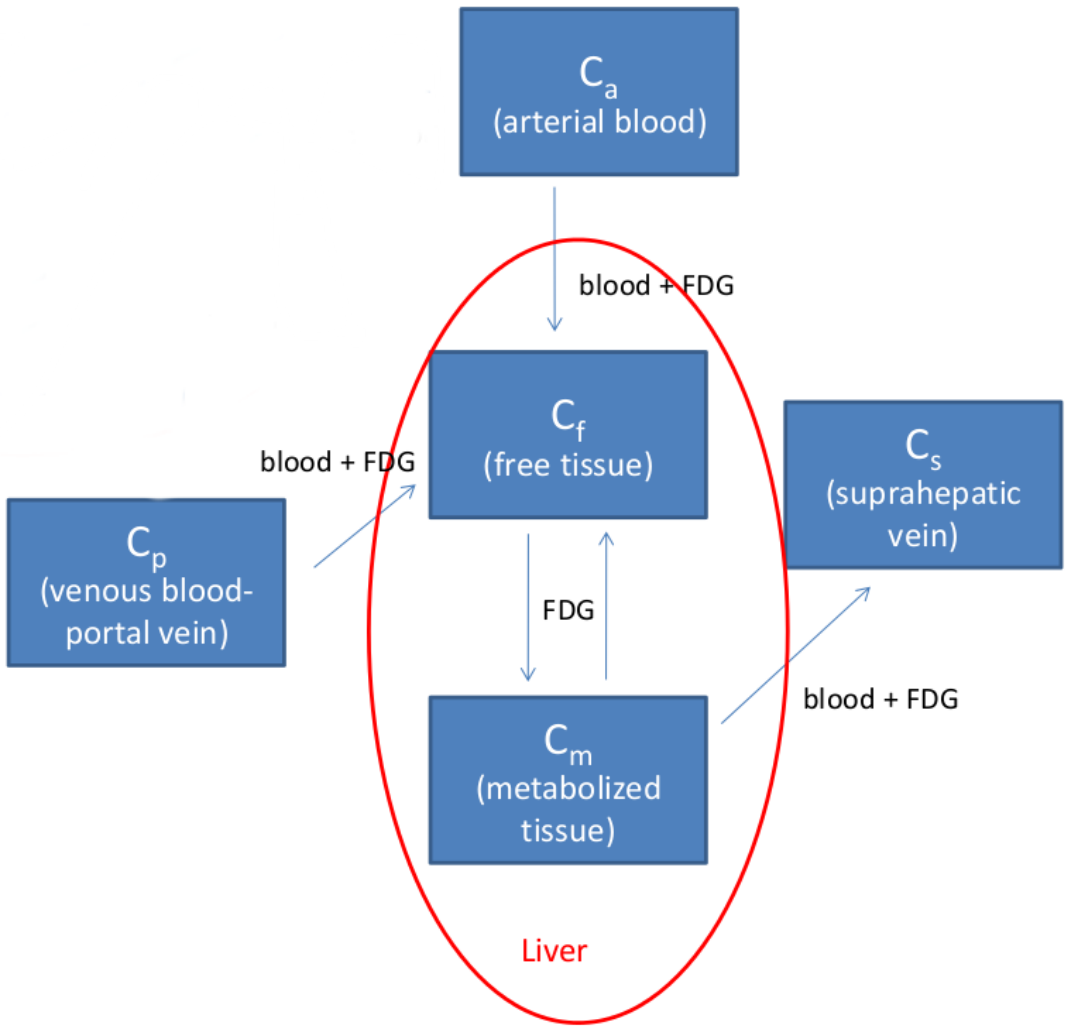
metabolism: tissue

liver - 1

- liver both stores and releases glucose
- the need to store or release glucose is signaled by insulin
- two possible therapies against insulin malfunction
  1. look for drugs that mimic insulin
  2. look for drugs that regulate glucose release from liver: **metformin**

liver - 2

(garbarino, vivaldi, buschiazzo, delbary, marini, caviglia, piana and sambuceti, *european journal of nuclear medicine and molecular imaging research*, 2015)



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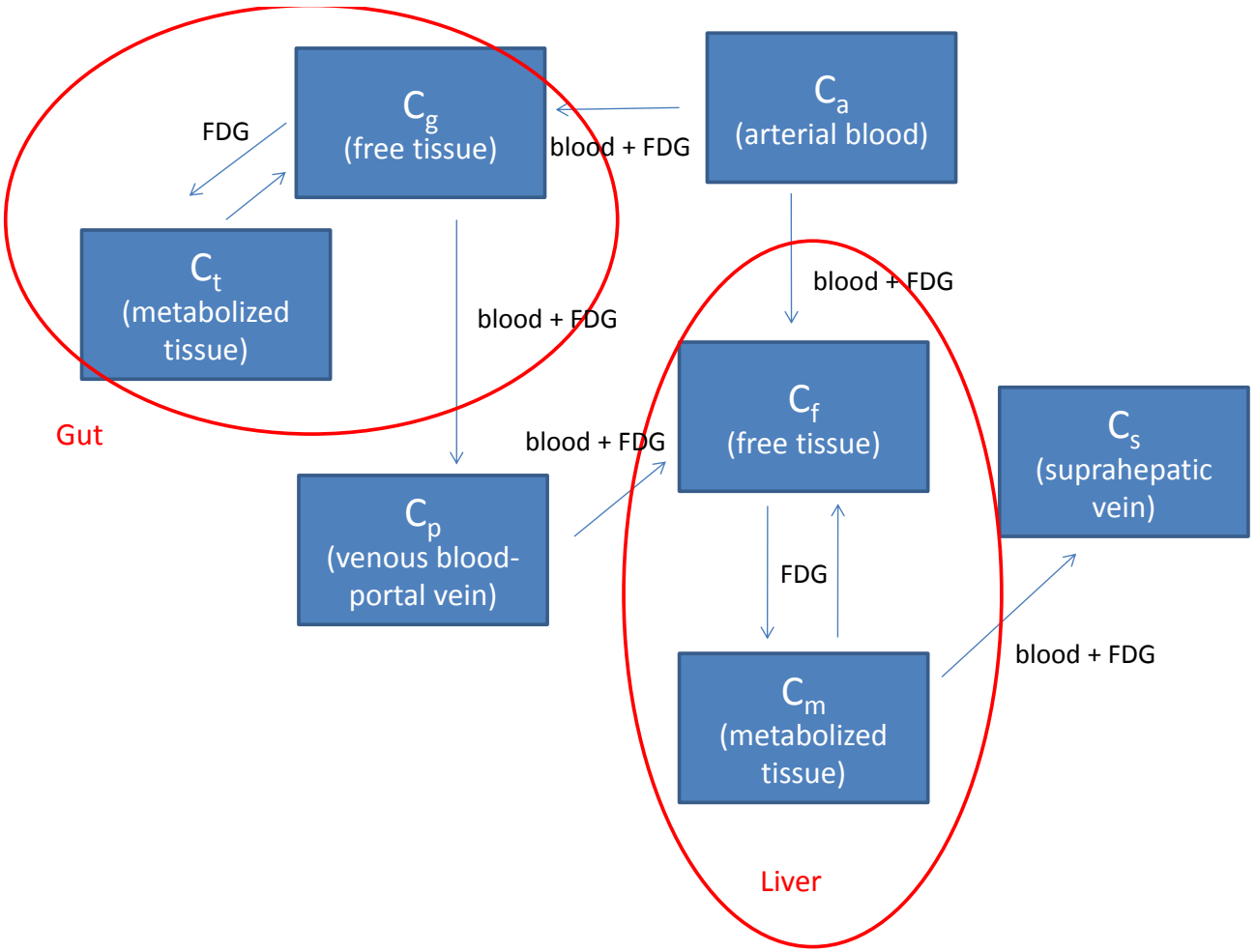
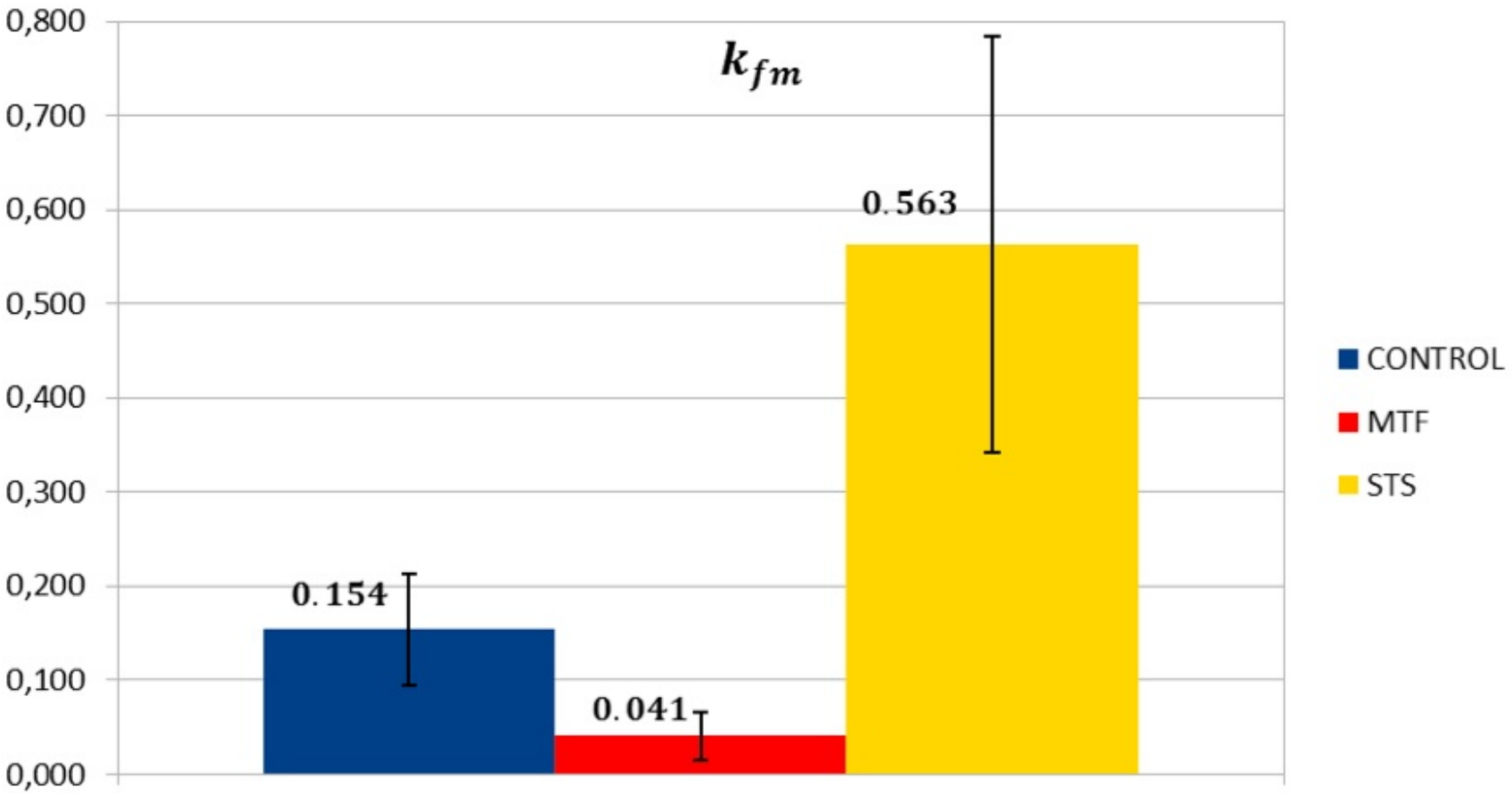


liver - 4


0,800
0,700
0,600
0,500
0,400
0,300
0,200
0,100
0,000
k_{fm}
0.563
0.154
0.041
CONTROL
MTF
STS

parametric imaging - 1

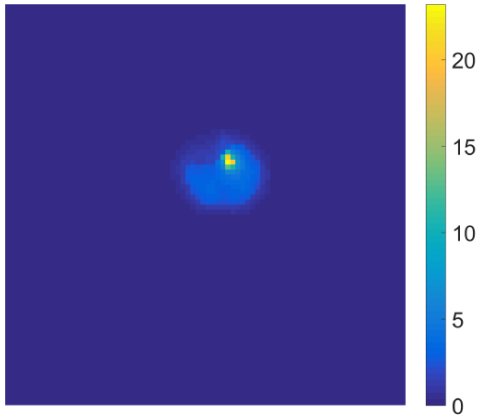
(scussolini, garbarino, sambuceti, caviglia and piana, *inverse problems*, 2017)

is it possible to solve the compartmental inverse problem pixel-wise?

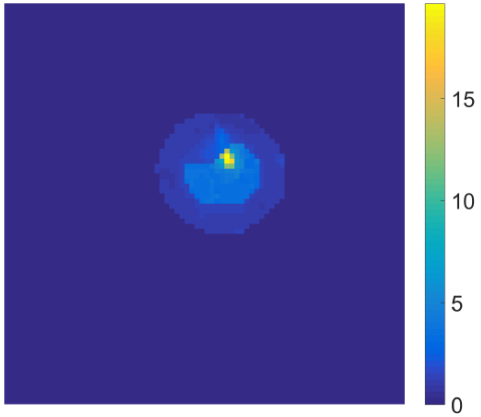
numerical scheme:

1. gaussian smoothing (to increase the signal-to-noise ratio)
2. segmentation (to automatically identify the region of physiological interest)
3. pixel-wise regularized gauss-newton inversion of the nuclear data

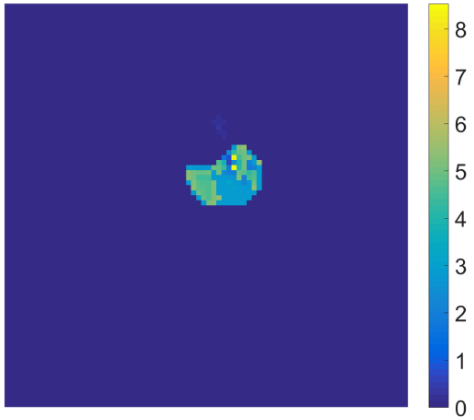
parametric imaging - 2



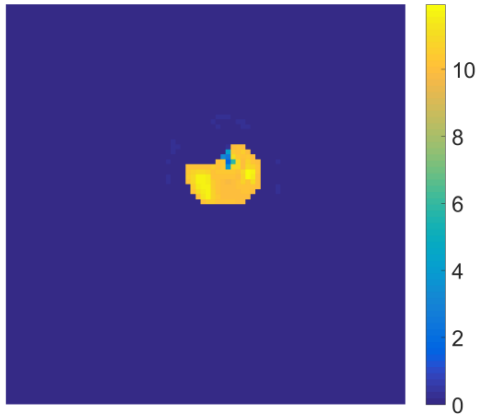
(a) k_{fb} e k_{fa}



(b) k_{bf} e k_{vf}

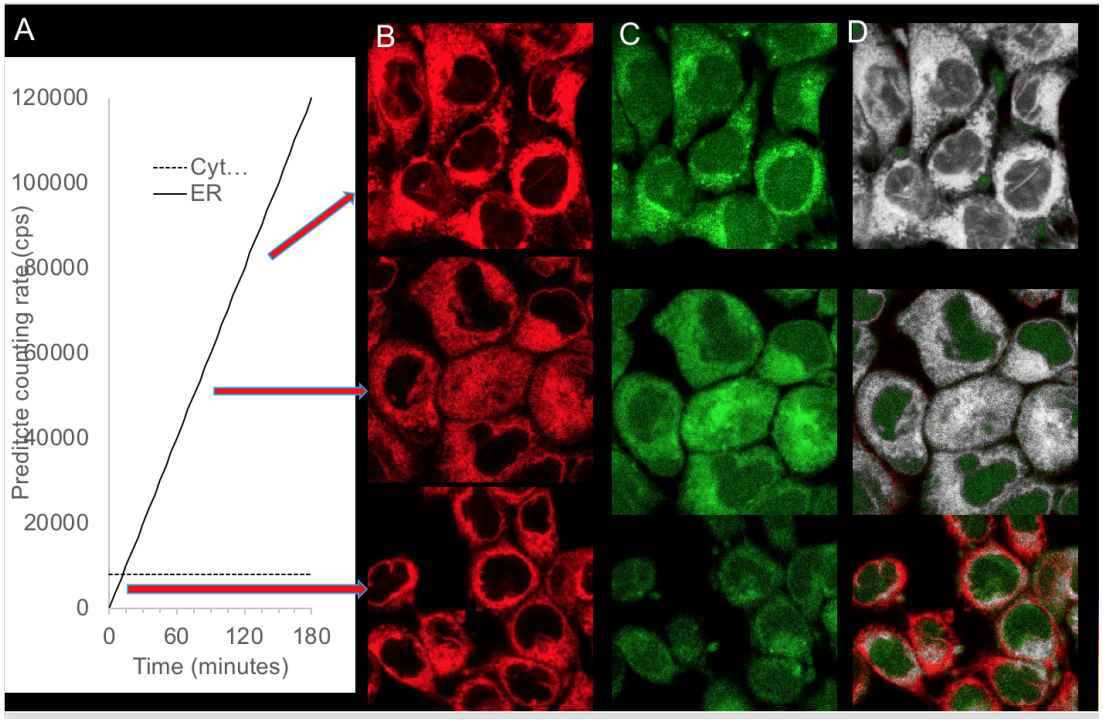


(c) k_{mf}

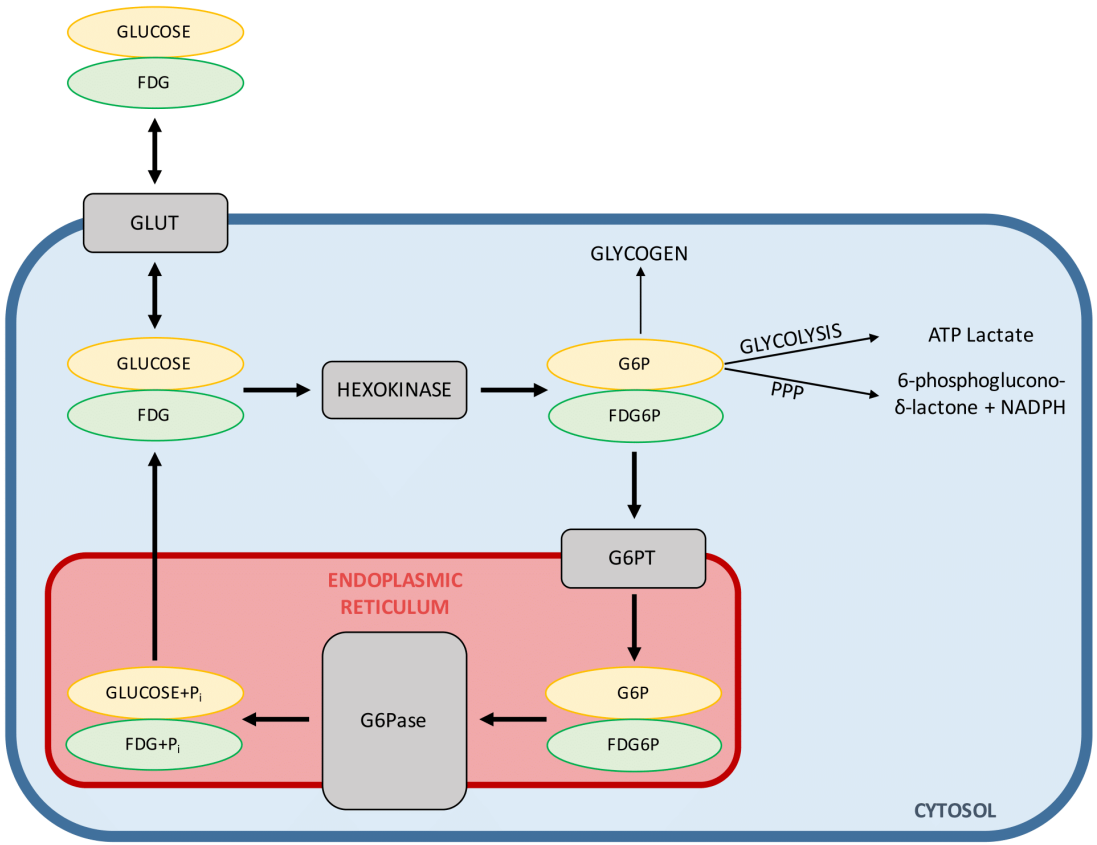


(d) k_{fm}

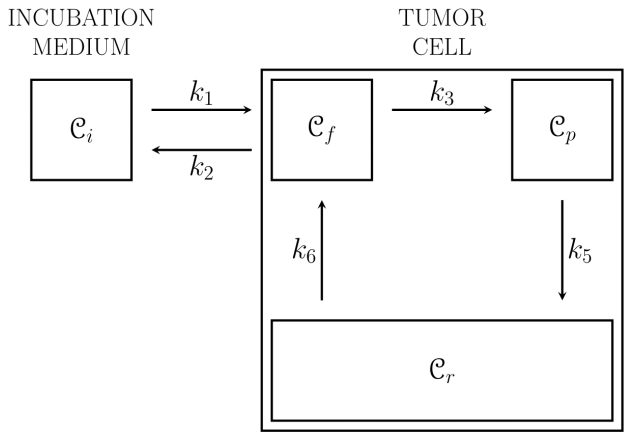
a (possible) breakthrough



a new model - biochemistry



a new model - data and unknowns

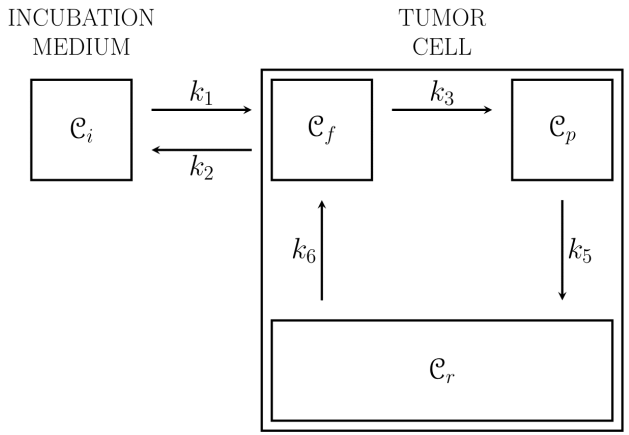


unknowns: five kinetic parameters (1/min) mimicking the actions of the enzymes GLUT, HK, G6PT, G6Pase

input data:

- the input function C_b
- the overall FDG concentration in the tumor: $C_{meas} = C_f + C_p + C_r$ where
  - C_f is the cytosolic free tracer
  - C_p is the cytosolic phosphorylated tracer
  - C_r is the phosphorylated tracer in the endoplasmic reticulum

forward problem



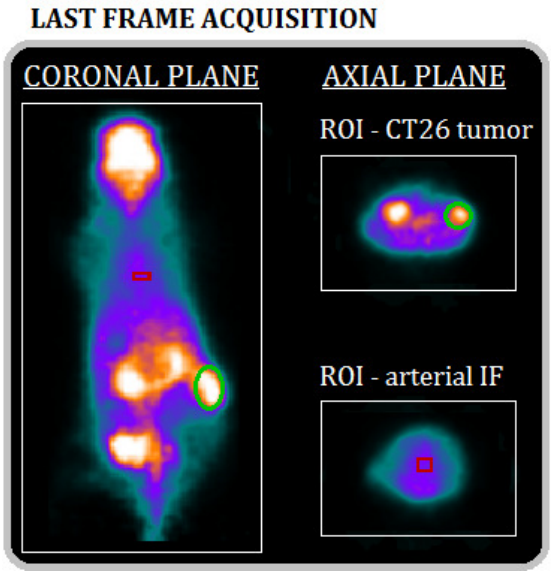
$$\dot{C} = MC + k_1 W$$

$$M = \begin{pmatrix} -(k_2 + k_3) & 0 & k_6 \\ k_3 & -k_5 & 0 \\ 0 & k_5 & -k_6 \end{pmatrix} \qquad C = \begin{pmatrix} C_f \\ C_p \\ C_r \end{pmatrix} \qquad W(t) = \begin{pmatrix} C_b(t) \\ 0 \\ 0 \end{pmatrix}$$

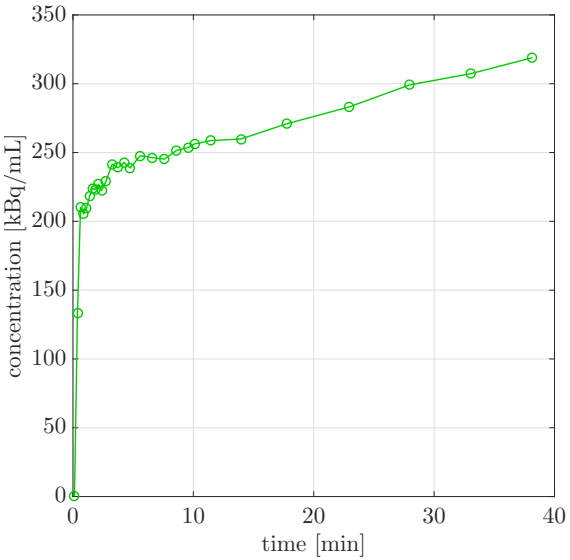
$$C_{meas} := C_f + C_p + C_r = k_1 \alpha^T \int_0^t C_b(u) \exp((t-u)M) e_1 \, du$$

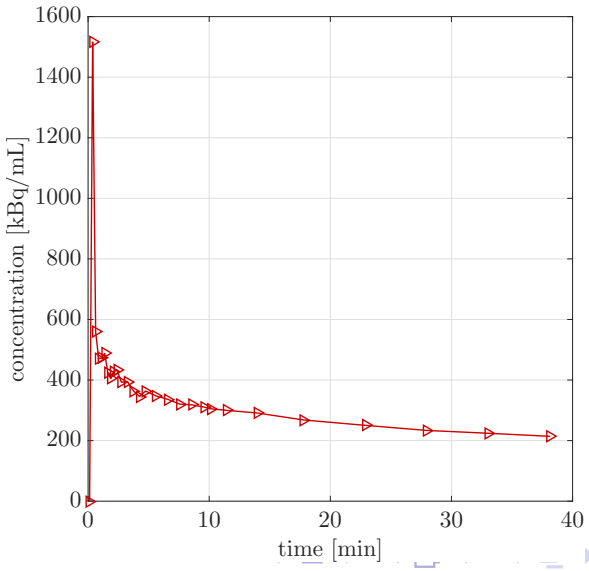
note: uniqueness holds (scussolini and caviglia, *j. math. biol.*, submitted)

CT26 - 1

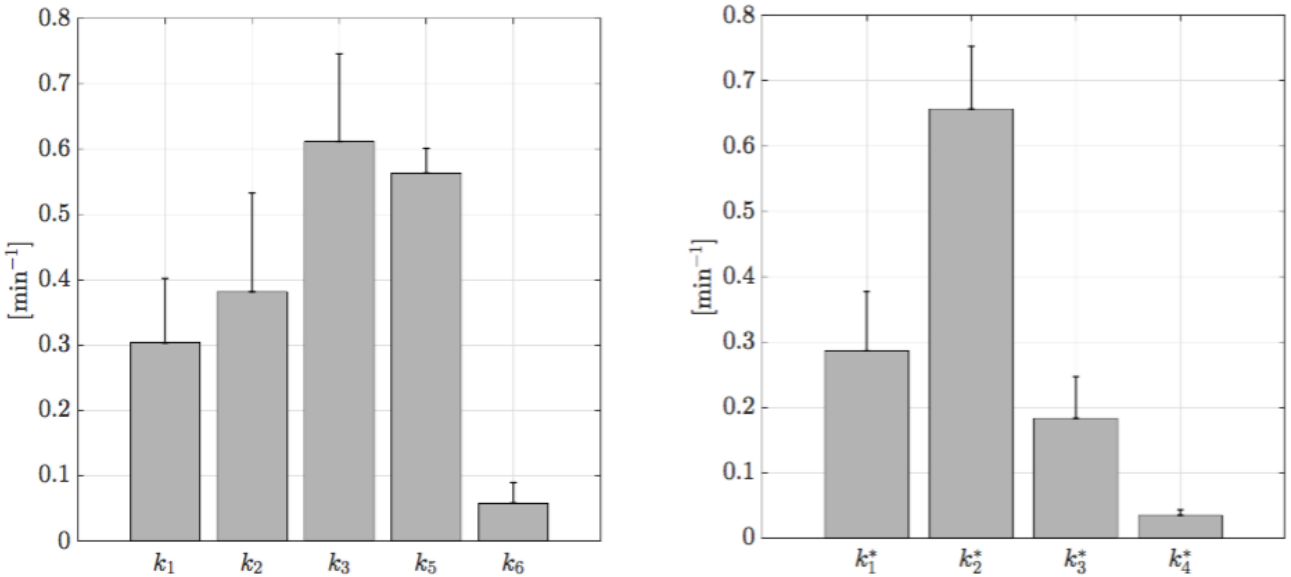


(a) Mouse model - ROIs





CT26 - 2



experimental $k_3 = 0.91 \pm 0.12$