DCE-imaging biomarker construction in cancer treatment

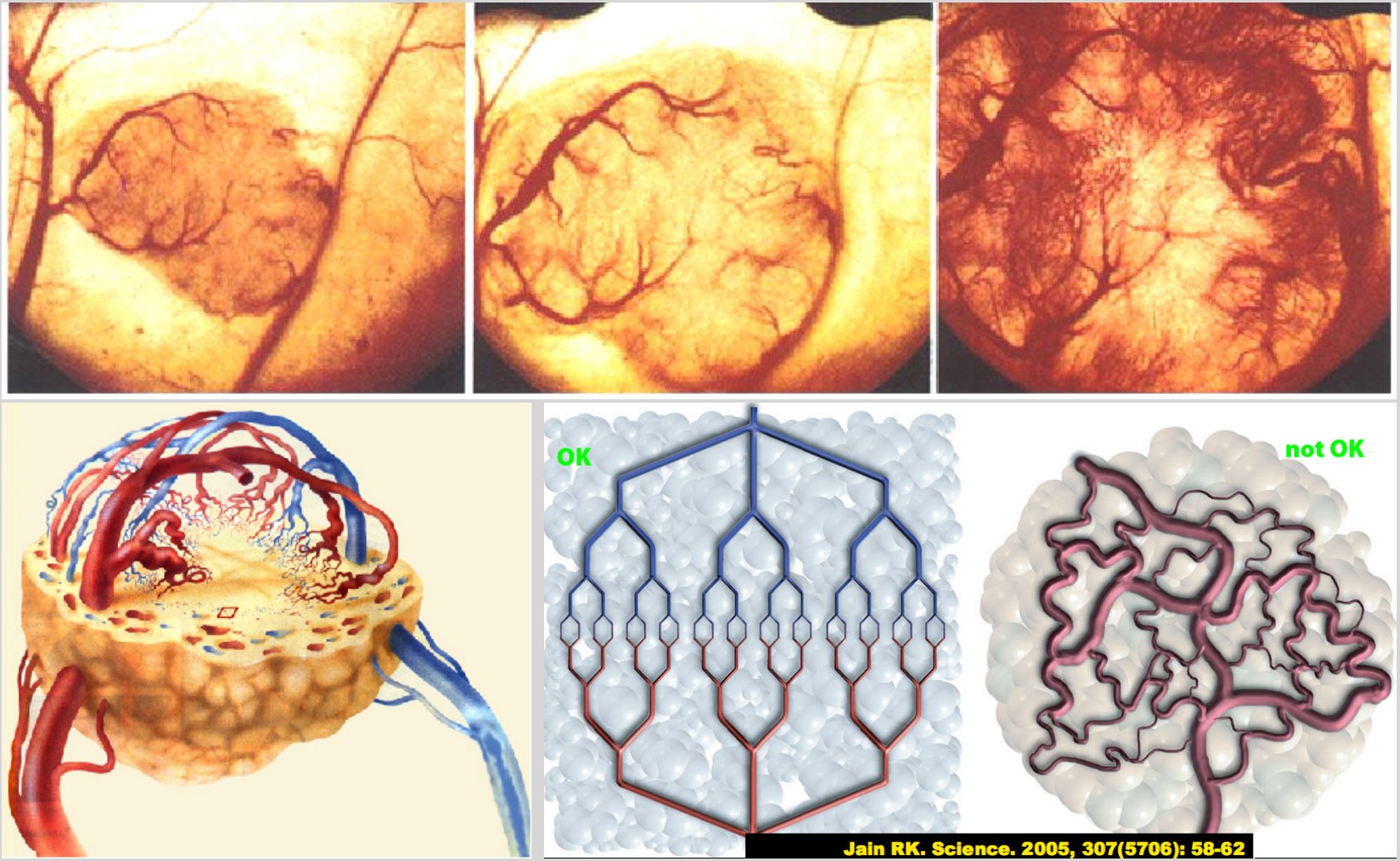
Statistical tools

Yves Rozenholc
USPC - Université Paris Descartes
Faculté de Pharmacie
MERIT - UMR IRD 216

http://up5.fr/rozenholc

Angiogenesis in cancer with C-A Cuénod (HEGP - LRI)

Angiogenesis : growth of new blood vessels from pre-existing vessels.



Angiogenesis in cancer with C-A Cuénod (HEGP - LRI)

IDEA: **An early 90's point of view**

$$\textbf{tumor} \rightleftharpoons \textbf{growth}\oplus \rightleftharpoons \textbf{energy} \rightleftharpoons \textbf{glucose} \rightleftharpoons \textbf{vascularization}\oplus$$

"Reducing angiogenesis will asphyxiate the tumor".

Angiogenesis in cancer with C-A Cuénod (HEGP - LRI)

IDEA: **An early 90's point of view**

$$\textbf{tumor} \rightleftharpoons \textbf{growth}\oplus \rightleftharpoons \textbf{energy} \rightleftharpoons \textbf{glucose} \rightleftharpoons \textbf{vascularization}\oplus$$

"Reducing angiogenesis will asphyxiate the tumor".

An interesting but unfortunately wrong idea

However, penalizing angiogenesis induces:

- **a regularization of the tumor blood pathways,**
- **an improvement of the tumor vessel efficiency.**

Angiogenesis in cancer with C-A Cuénod (HEGP - LRI)

IDEA: **An early 90's point of view**

$$\textbf{tumor} \rightleftharpoons \textbf{growth}\oplus \rightleftharpoons \textbf{energy} \rightleftharpoons \textbf{glucose} \rightleftharpoons \textbf{vascularization}\oplus$$

"Reducing angiogenesis will asphyxiate the tumor".

An interesting but unfortunately wrong idea

However, penalizing angiogenesis induces:

- **a regularization of the tumor blood pathways,**
- **an improvement of the tumor vessel efficiency.**

Current point of view

At least anti-angiogenesis treatments may help to bring chemical weapons inside the tumor.

"Anti-angiogenesis treatments help to fight tumors from inside".

Materials

A Dynamic Contrast Enhancement - CT (DCE-CT) example

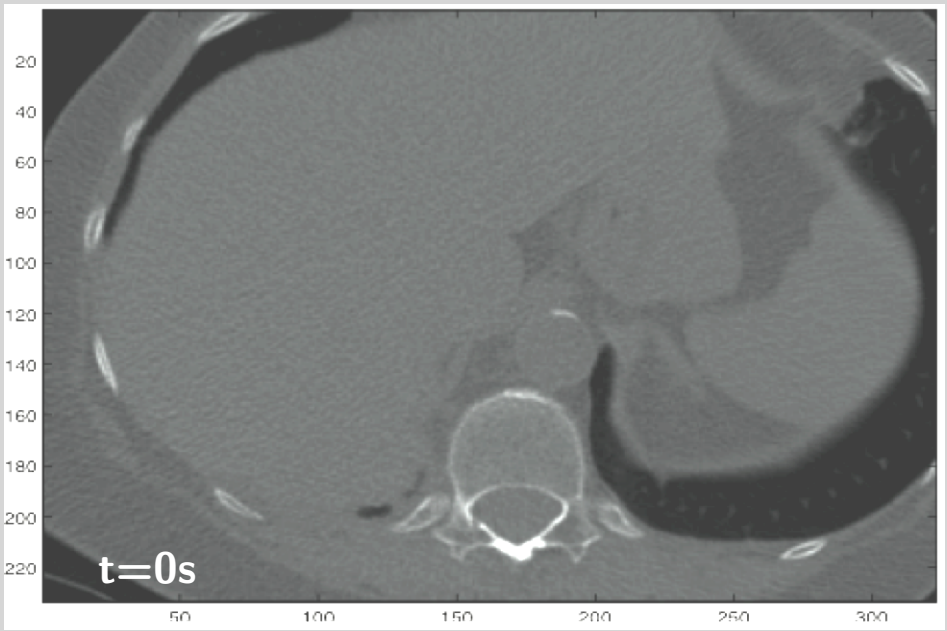
(Loading ... please wait)

Axial CT image of the abdomen showing a liver metastasis.
Follow-up of a 80ml injection from Xénétix *as contrast agent.*

DCE-CT experiment with C-A Cuénod (HEGP - LRI)

Follow-up of a contrast agent bolus injection via DCE Computerized Tomography

About 50 images in 100 secondes with very low X-ray dose

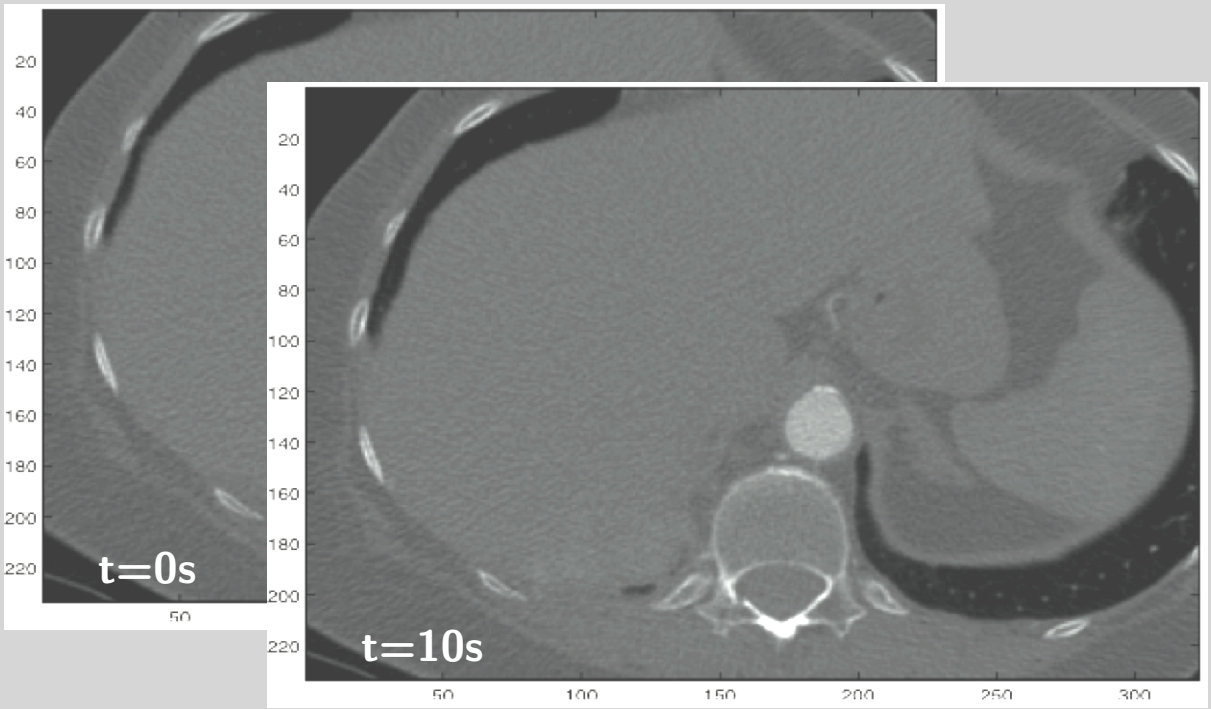


before injection

DCE-CT experiment with C-A Cuénod (HEGP - LRI)

Follow-up of a contrast agent bolus injection via DCE Computerized Tomography

About 50 images in 100 secondes with very low X-ray dose

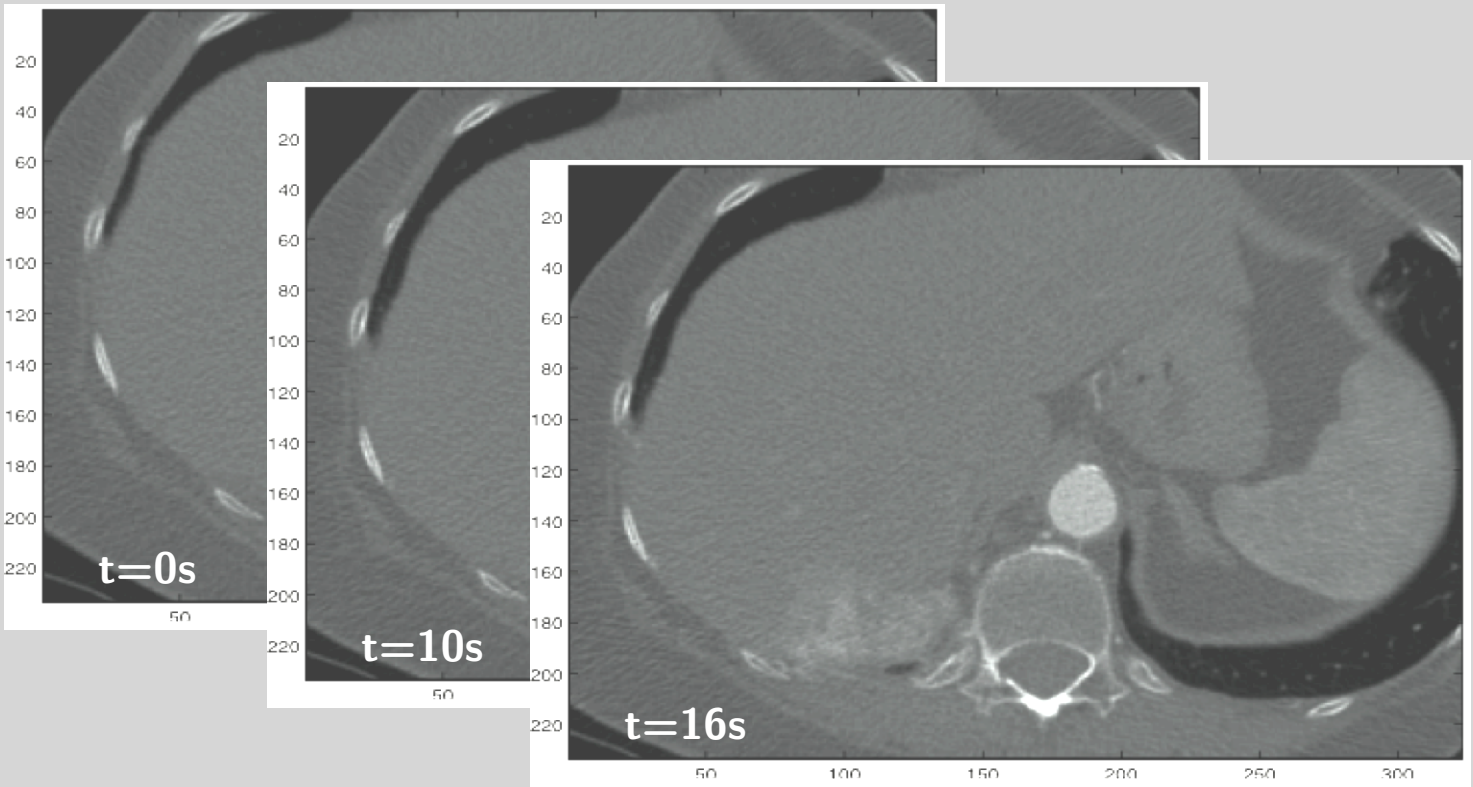


arterial phase

DCE-CT experiment with C-A Cuénod (HEGP - LRI)

Follow-up of a contrast agent bolus injection via DCE Computerized Tomography

About 50 images in 100 secondes with very low X-ray dose

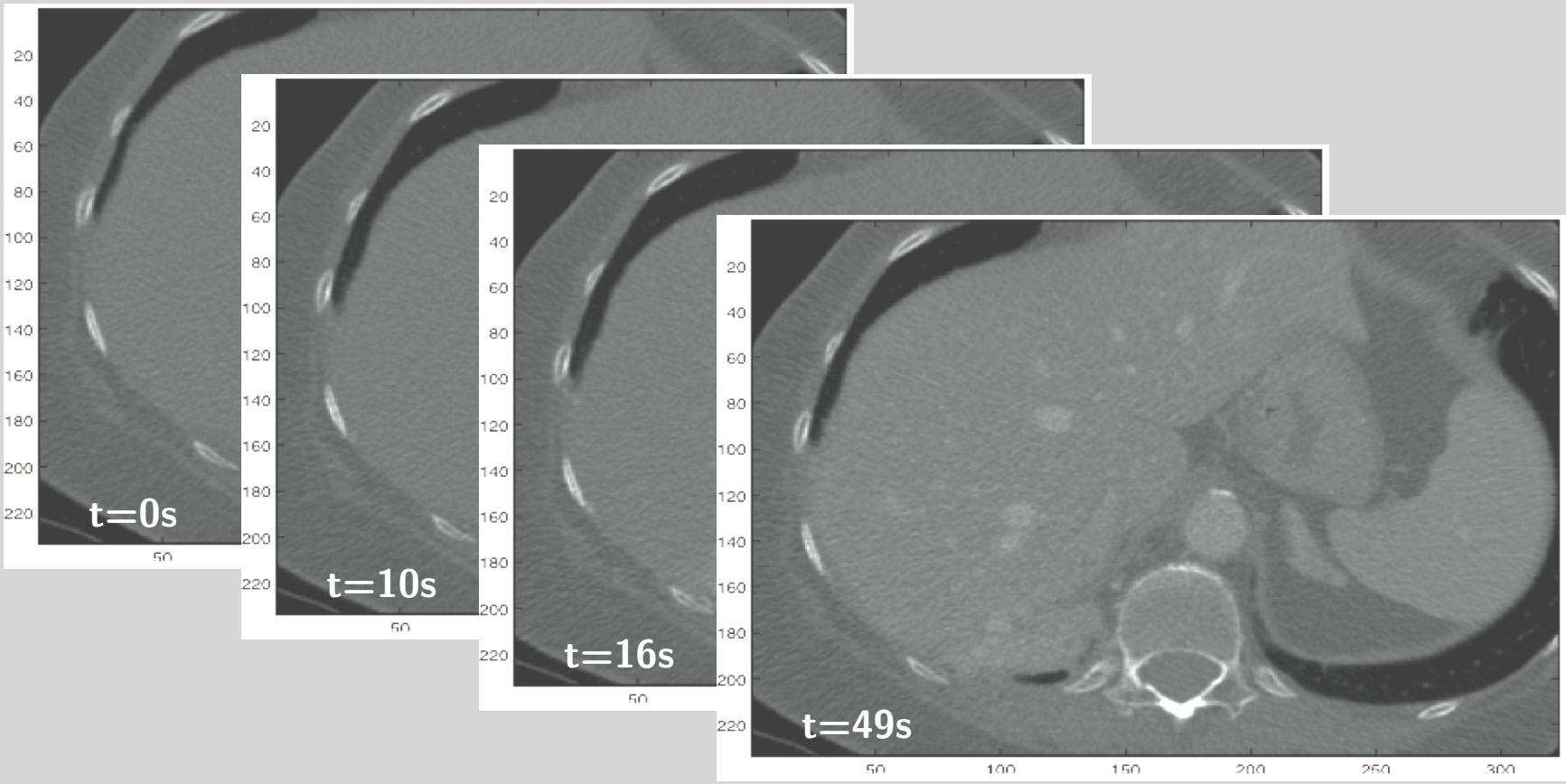


after arterial phase

DCE-CT experiment with C-A Cuénod (HEGP - LRI)

Follow-up of a contrast agent bolus injection via DCE Computerized Tomography

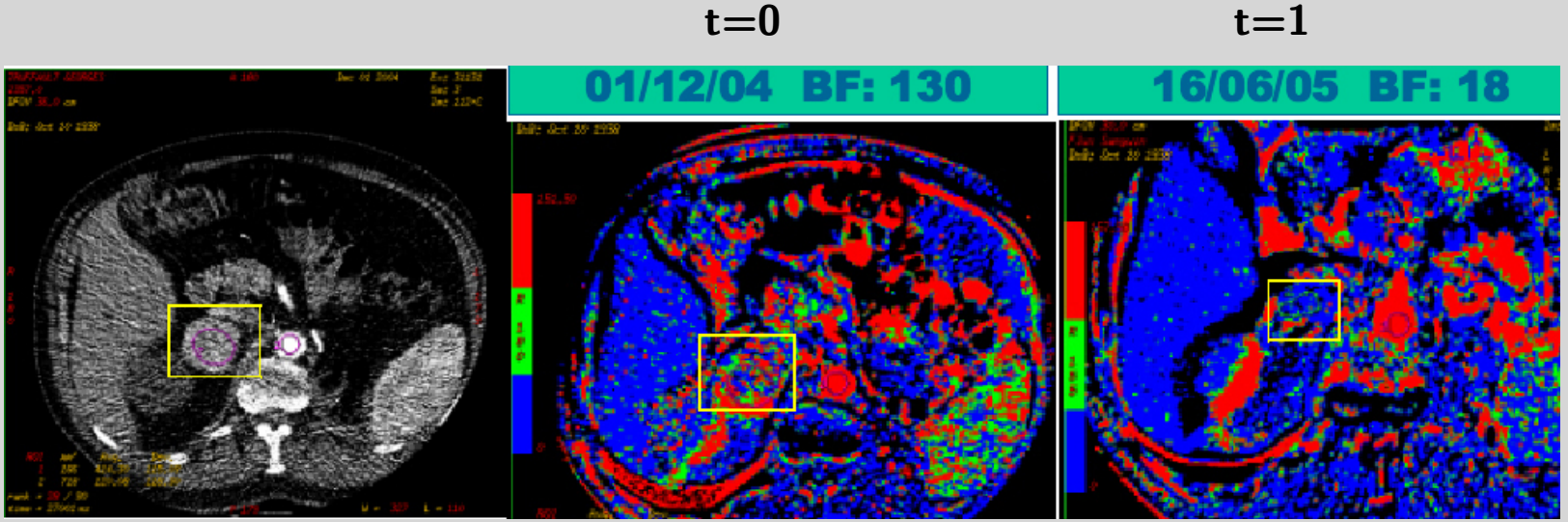
About 50 images in 100 secondes with very low X-ray dose



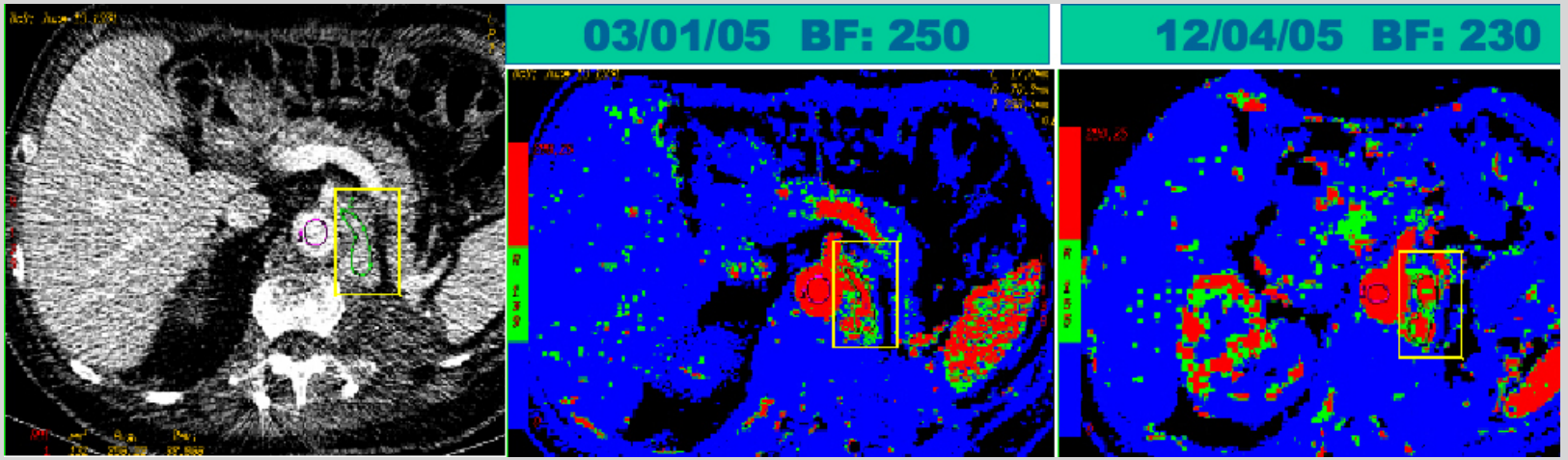
veinous phase

Building biomarker in cancer treatment

Discriminating between "responder" and "not responder"



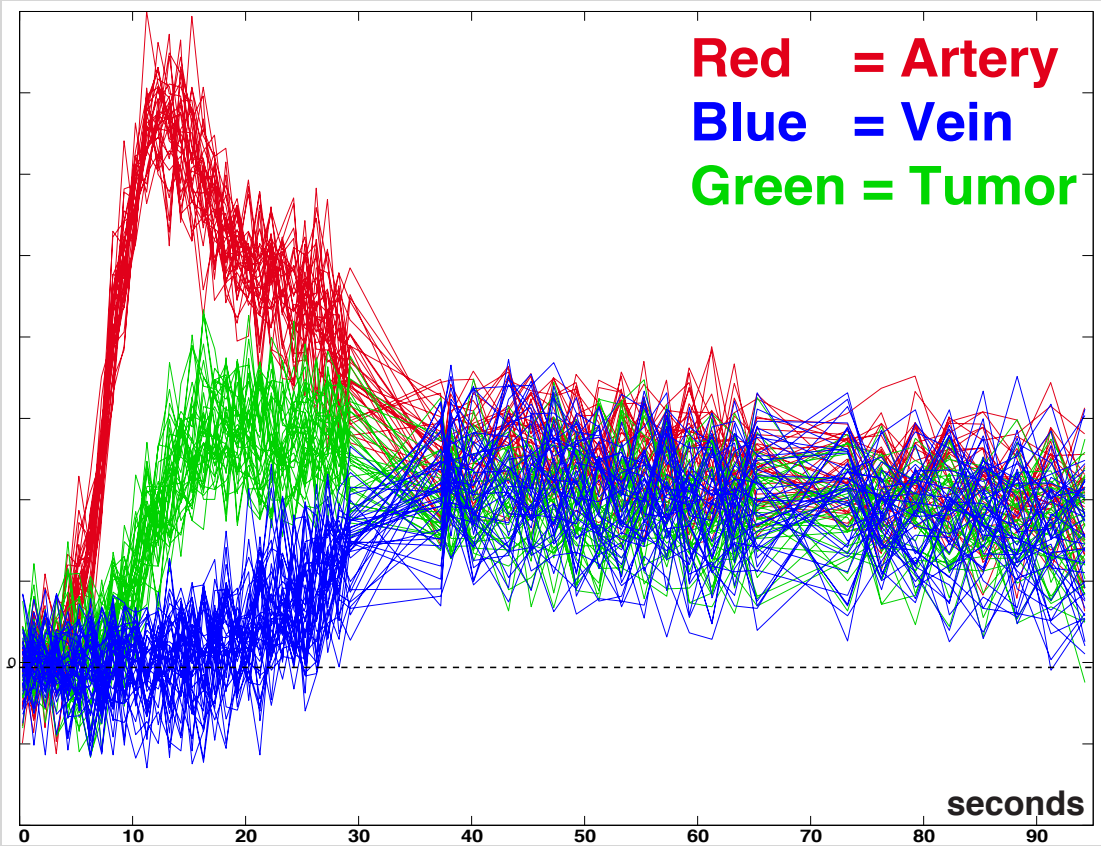
Responder



Not-Responder

A noisy problem

Typical enhancements



Model : $Q^x(t_i) = q^x(t_i) + \sigma\varepsilon_i^x,\ i = 1 \ldots n,$

Image made of time-series

Automatic clustering for DCE with Fuchen Liu (PhD)

Problem: We assume that the image $\mathcal{X}$ is made of few clusters that we aim at recover

- $\mathcal{X} = C_1 \cup \ldots \cup C_K$;
- if $x \in C_k$ for $k = 1, \ldots, K$, then $\mathbb{E}(Q^x) = q^x =: q_k$;
- if $k \neq \ell$, then $C_k \cap C_\ell = \varnothing$ and $q_k \neq q_\ell$.

Automatic clustering for DCE with Fuchen Liu (PhD)

Problem: We assume that the image $\mathcal{X}$ is made of few clusters that we aim at recover

- $\mathcal{X} = C_1 \cup \ldots \cup C_K$;
- if $x \in C_k$ for $k = 1, \ldots, K$, then $\mathbb{E}(Q^x) = q^x =: q_k$;
- if $k \neq \ell$, then $C_k \cap C_\ell = \varnothing$ and $q_k \neq q_\ell$.

Key idea: Build a test such that "=" should be the research hypothesis H_1.

$$H_0^{xy} : d^{xy} \neq \vec{0} \qquad \text{v.s.} \qquad H_1^{xy} : d^{xy} = \vec{0}$$

where $d^{xy} = q^y - q^x$

Automatic clustering for DCE with Fuchen Liu (PhD)

Problem: We assume that the image $\mathcal{X}$ is made of few clusters that we aim at recover

- $\mathcal{X} = C_1 \cup \ldots \cup C_K$;
- if $x \in C_k$ for $k = 1, \ldots, K$, then $\mathbb{E}(Q^x) = q^x =: q_k$;
- if $k \neq \ell$, then $C_k \cap C_\ell = \varnothing$ and $q_k \neq q_\ell$.

Key idea: Build a test such that "=" should be the research hypothesis H_1.

$$H_0^{xy} : d^{xy} \neq \vec{0} \qquad \text{v.s.} \qquad H_1^{xy} : d^{xy} = \vec{0}$$

where $d^{xy} = q^y - q^x$

Intersection-Union Test: (π_k is the projection on a time-partition with 2^k bins)

$$H_0 = \bigcup_k (H_0^k : \|\pi_k(d^{xy})\|^2 \neq 0) \qquad \text{versus} \qquad H_1 = \bigcap_k (H_1^k : \|\pi_k(d^{xy})\|^2 = 0).$$

Automatic clustering for DCE with Fuchen Liu (PhD)

Problem: We assume that the image $\mathcal{X}$ is made of few clusters that we aim at recover

- $\mathcal{X} = C_1 \cup \ldots \cup C_K$;
- if $x \in C_k$ for $k = 1, \ldots, K$, then $\mathbb{E}(Q^x) = q^x =: q_k$;
- if $k \neq \ell$, then $C_k \cap C_\ell = \varnothing$ and $q_k \neq q_\ell$.

Key idea: Build a test such that "=" should be the research hypothesis H_1.

$$H_0^{xy} : d^{xy} \neq \vec{0} \qquad \text{v.s.} \qquad H_1^{xy} : d^{xy} = \vec{0}$$

where $d^{xy} = q^y - q^x$

Intersection-Union Test: (π_k is the projection on a time-partition with 2^k bins)

$$H_0 = \bigcup_k (H_0^k : \|\pi_k(d^{xy})\|^2 \neq 0) \qquad \text{versus} \qquad H_1 = \bigcap_k (H_1^k : \|\pi_k(d^{xy})\|^2 = 0).$$

Th. (Berger and Hsu,1996): If R_J are α-level rejection regions of H_0^k, then $R = \cap_k R_k$ is a α-level rejection region for H_0. It folllows that if p_k is the p-value for H_0^k, then the rejection region $R = \cap_k R_k$ has $\max_k(p_k)$ for p-value.

Idea: Use $p(x : y) := \max_k(p_k^{xy})$ as a **dissimilarity measure** in a hierarchical approach.

Automatic clustering for DCE with Fuchen Liu (PhD)

using multiple equivalence test

Model: $Q^x(t_i) = q^x(t_i) + \sigma\varepsilon_i^x, \quad i = 1 \dots n,$ with i.i.d. ε_i^x. together with $Q^X = \sum_{x\in X} Q^x/n$

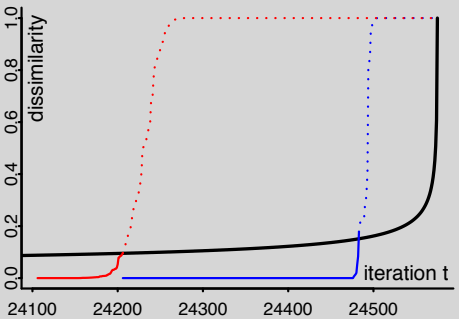
Rejection Area: $\exists k$ s.t. $\|\pi_k D^{XY}\|^2 \leqslant 2^K + \delta^2 - 2\sqrt{(2^K/n + 2\delta^2)\ln\alpha^{-1}}$ with $D^{XY} = \frac{Q^X - Q^Y}{\sigma\sqrt{1/|X| + 1/|Y|}}$

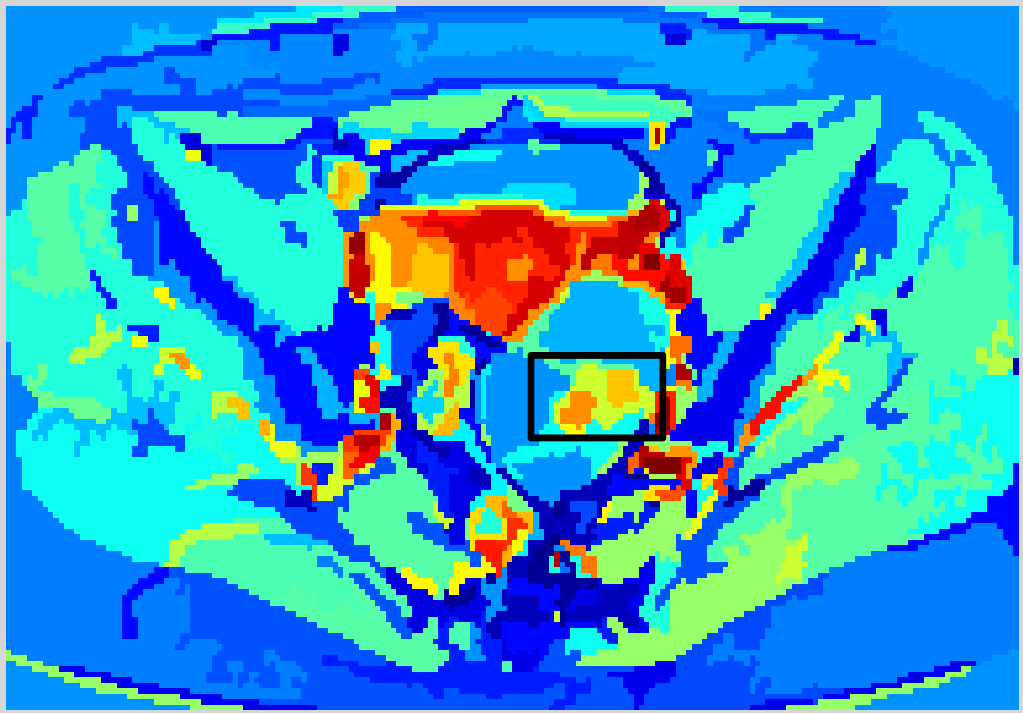
ensures that if $\|\pi_k d^{XY}\|^2 \leqslant n\delta$, X and Y are clusterized with probability $1-\alpha$.

Hierarchical clustering with p-values are used as dissimilarity measure

• clustering stops automatically by ensuring that the minimum p-value of s **different** clusters is smaller than $c_\alpha(s)$ with small probability α (type I error):

$$c_\alpha(s) = (1-(1-\alpha)^{2/s(s-1)})^{1/(K_0+1)}.$$





Automatic clustering for DCE with Fuchen Liu (PhD)

A two steps procedure to take into account local and global properties of the tissue/image

Local clustering:

- Starts from a partition made of all voxels as singletons;
- only consider **neighbors** in four directions: **n**orth, **s**outh, **e**ast, **w**est;
- At each iteration, merge two neighbor clusters with minimal dissimilarity measure.

Automatic clustering for DCE with Fuchen Liu (PhD)

A two steps procedure to take into account local and global properties of the tissue/image

Local clustering:

- Starts from a partition made of all voxels as singletons;
- only consider **neighbors** in four directions: **n**orth, **s**outh, **e**ast, **w**est;
- At each iteration, merge two neighbor clusters with minimal dissimilarity measure.

Global clustering: when local clustering stops, change the neighborhood structure in either:

- the neighbors of the neighbors
- all other clusters

Automatic clustering for DCE with Fuchen Liu (PhD)

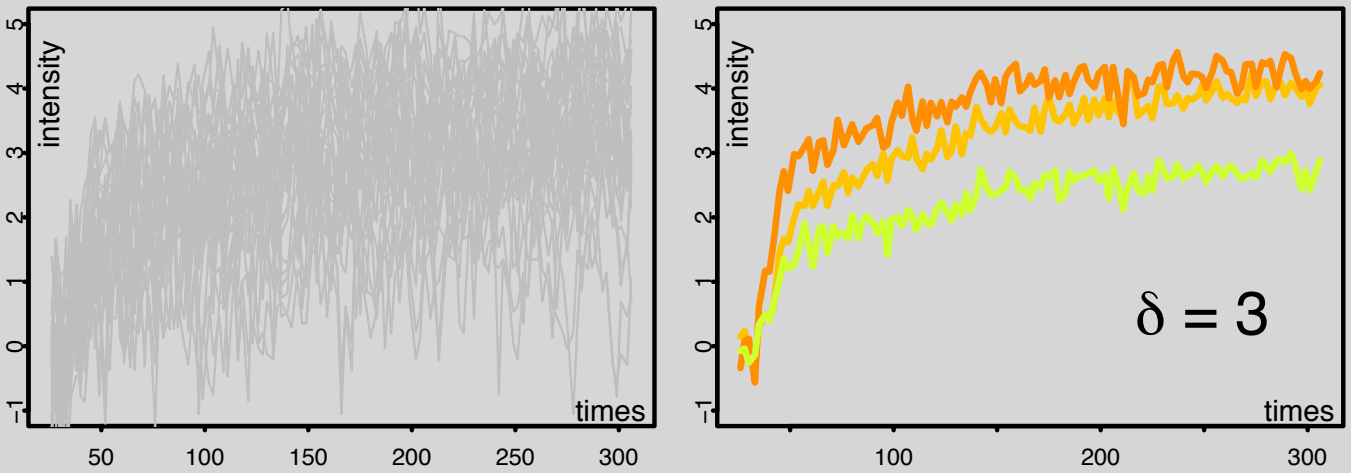
A two steps procedure to take into account local and global properties of the tissue/image

Local clustering:

- Starts from a partition made of all voxels as singletons;
- only consider **neighbors** in four directions: **n**orth, **s**outh, **e**ast, **w**est;
- At each iteration, merge two neighbor clusters with minimal dissimilarity measure.

Global clustering: when local clustering stops, change the neighborhood structure in either:

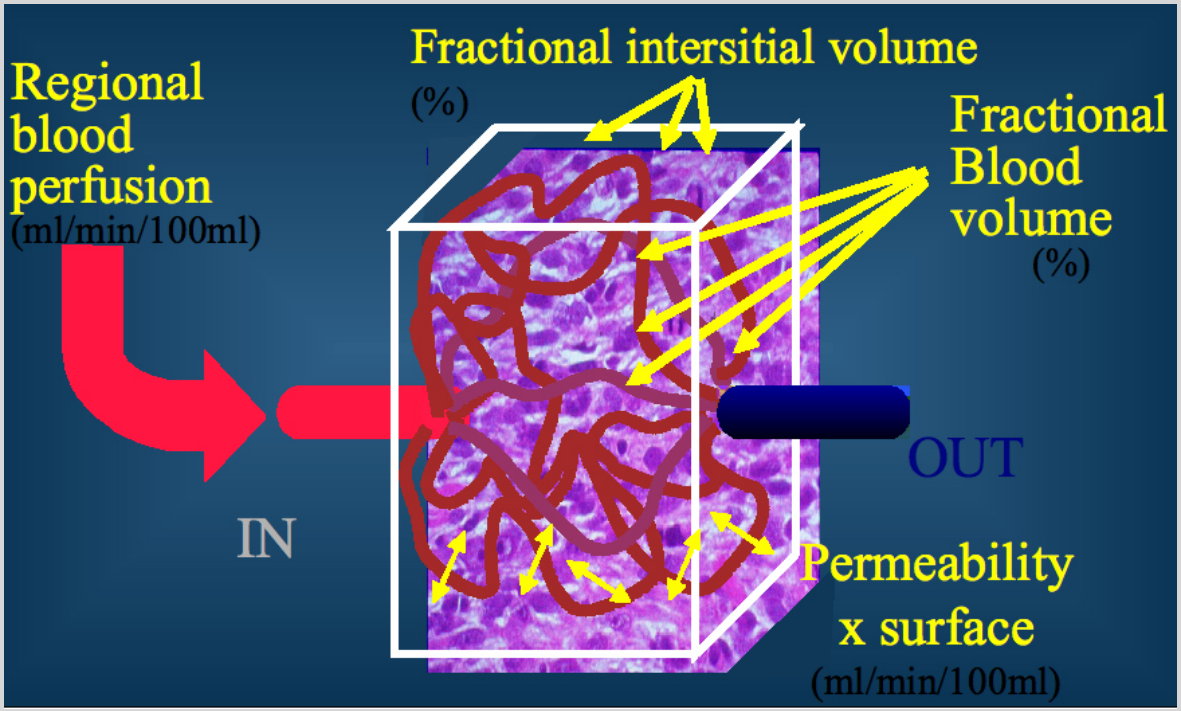
- the neighbors of the neighbors
- all other clusters



Take away message

Testing equality of dynamics helps to
clusterize homogeneous tissue
and
improve signal to noise ratio !

A parametric model for tissue microvascular circulation.

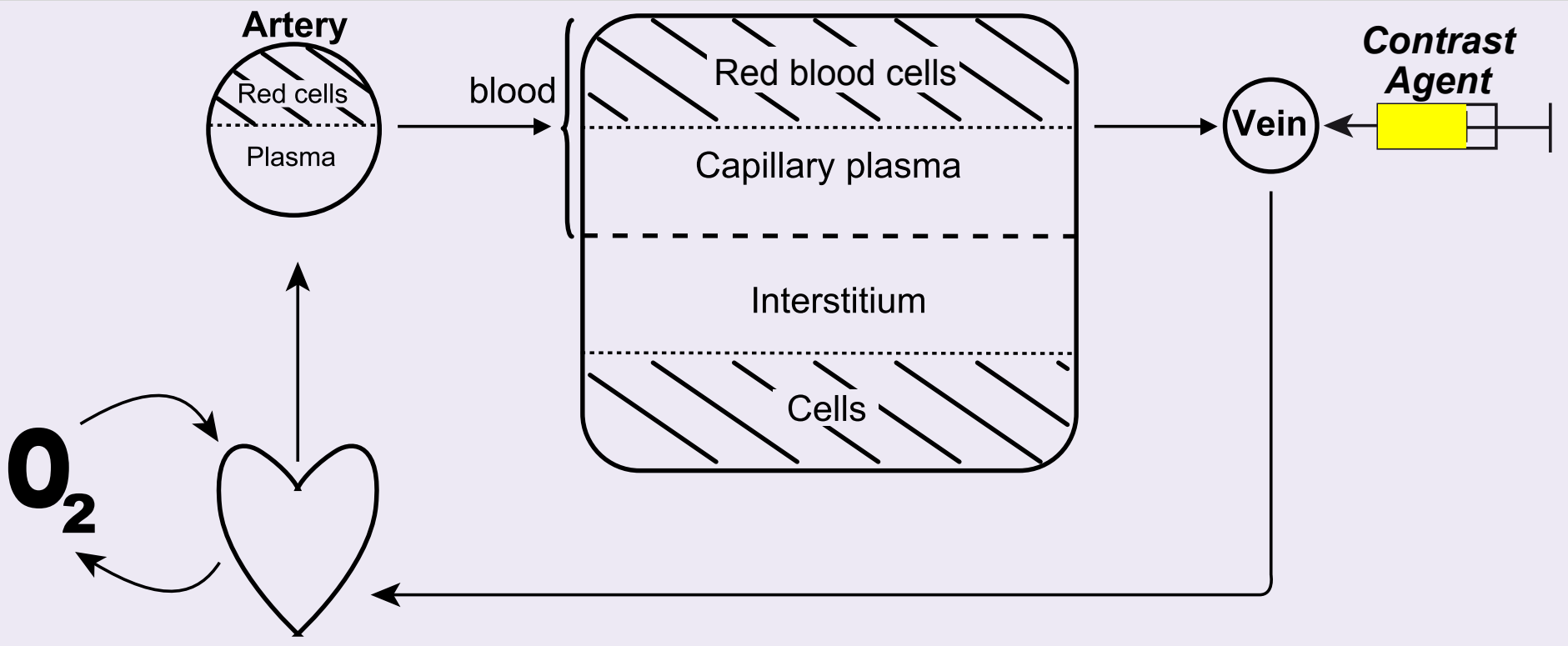


Quantities of interest are NOT related to

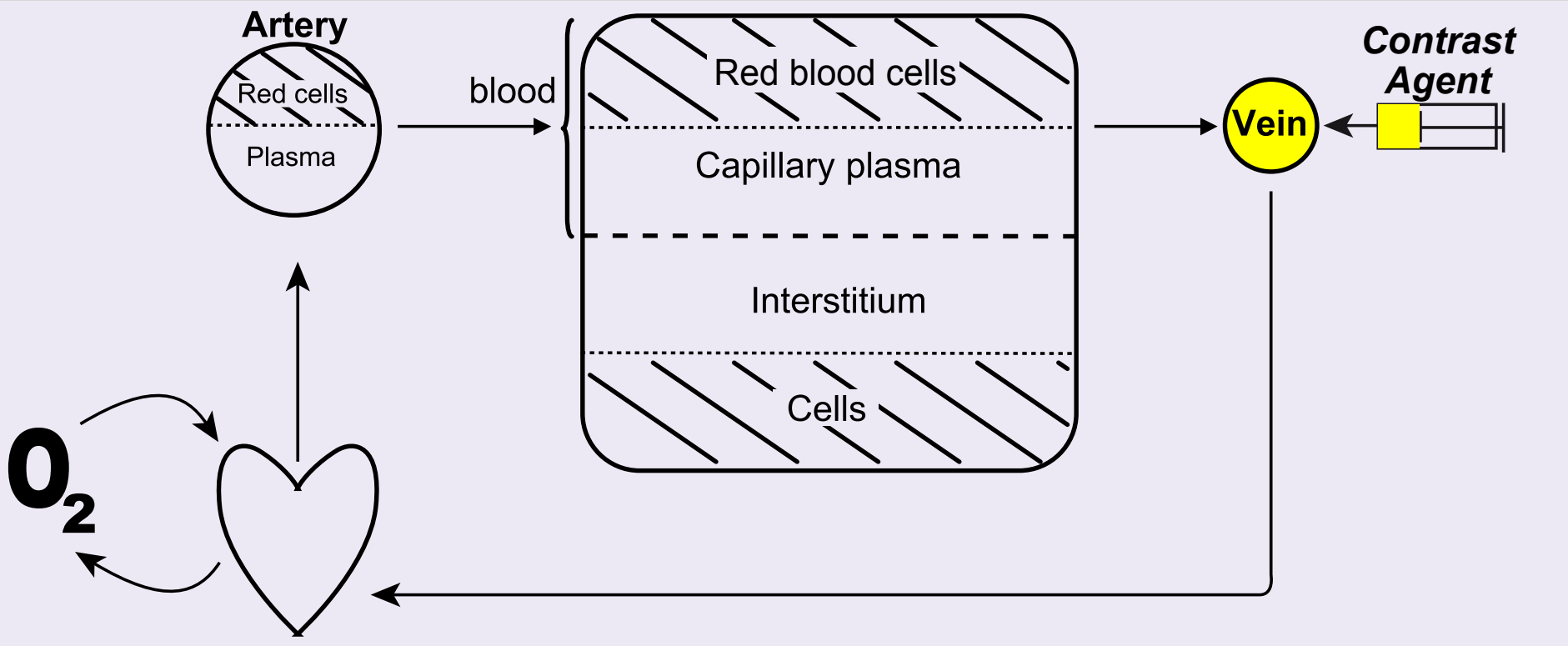
- blood input,
- contrast agent characteristics.

but are related to bio-medical descriptions of the microvascular circulation.

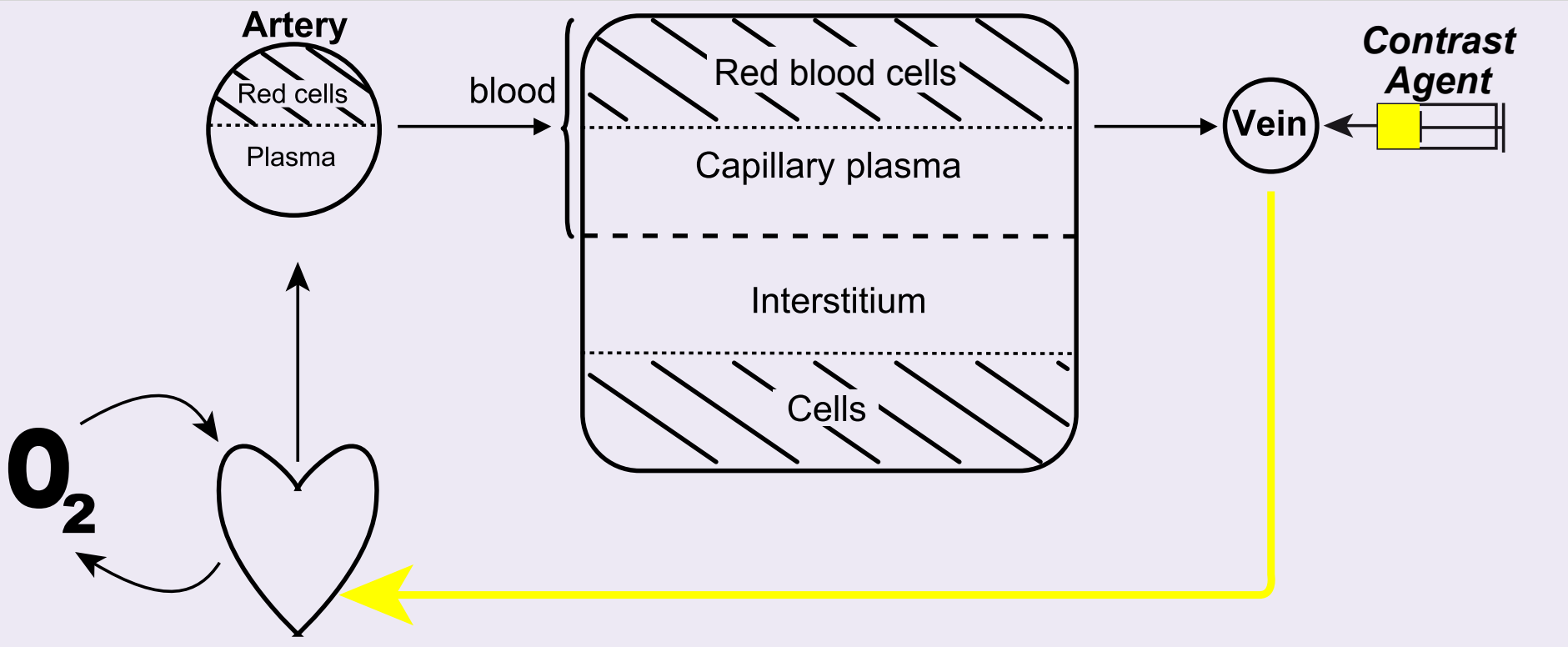
Parametric model for tissue microvascular circulation.



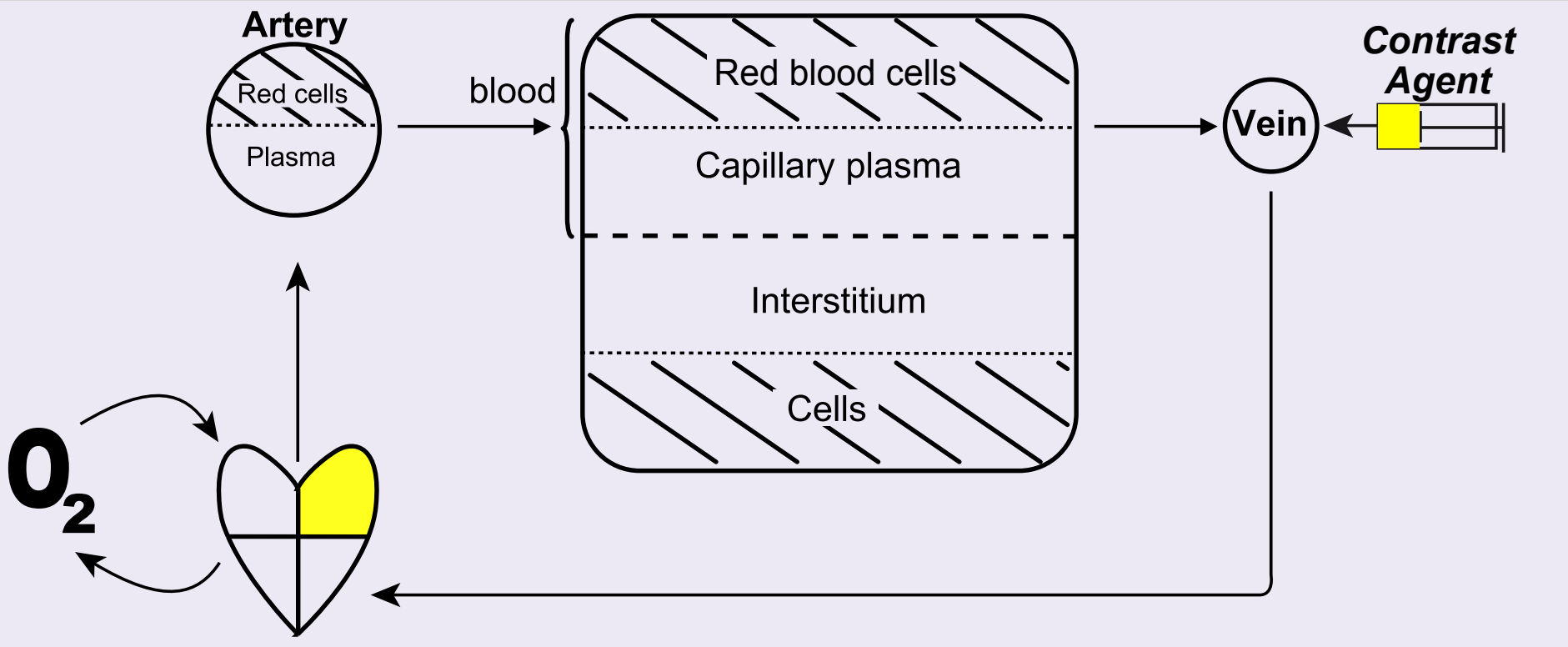
Parametric model for tissue microvascular circulation.



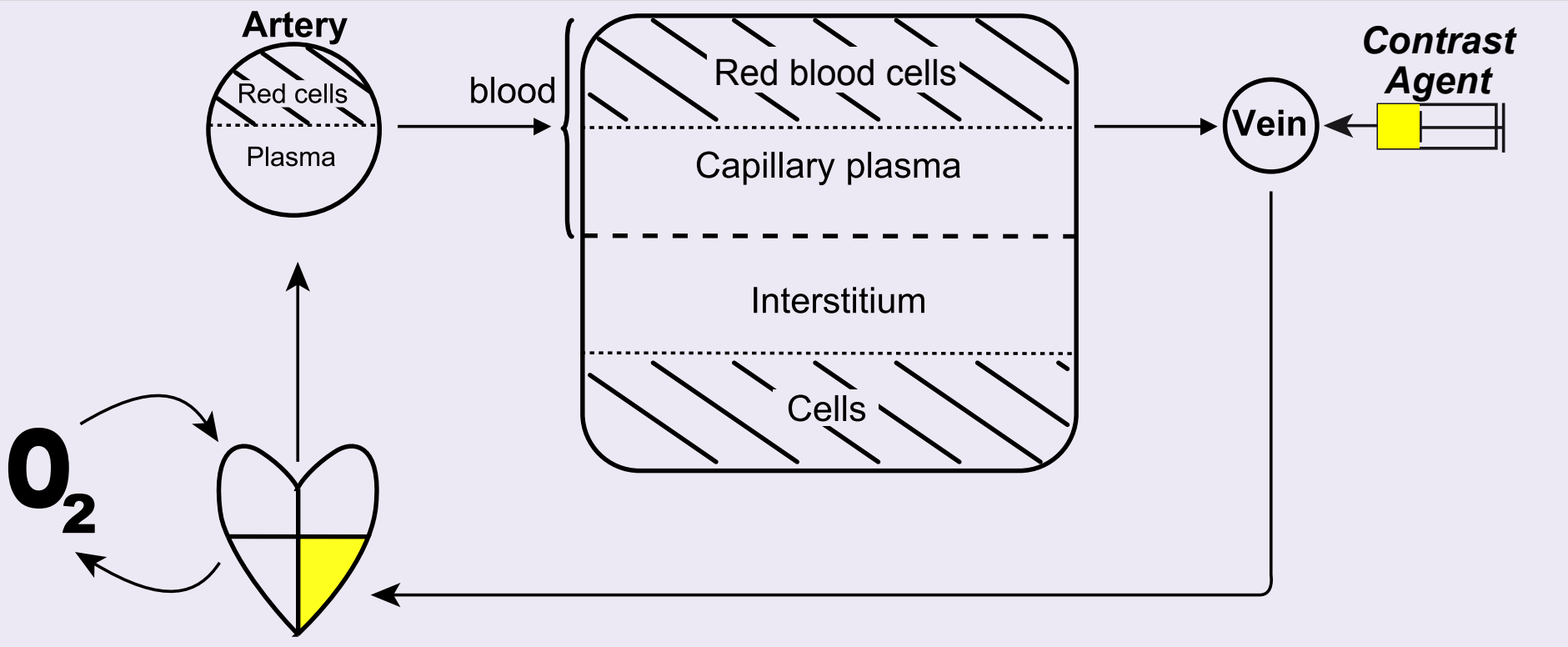
Parametric model for tissue microvascular circulation.



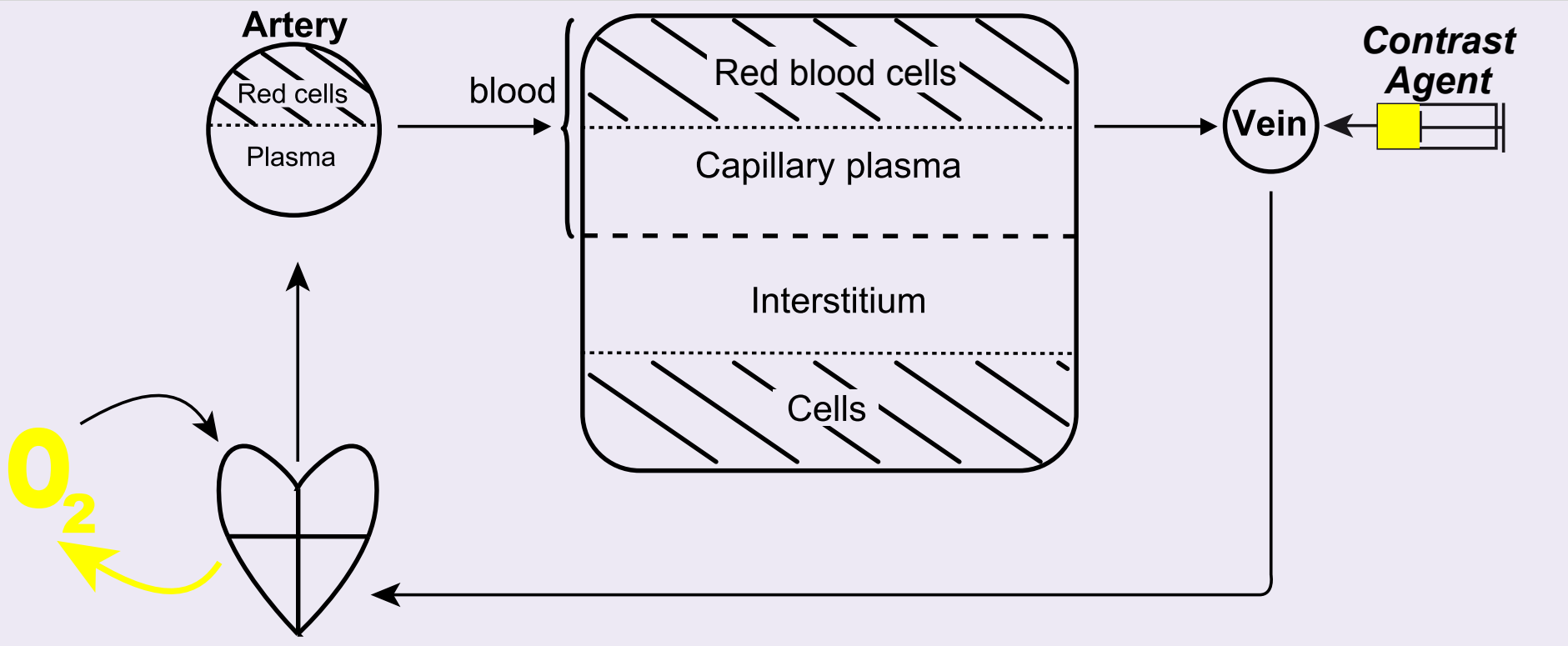
Parametric model for tissue microvascular circulation.



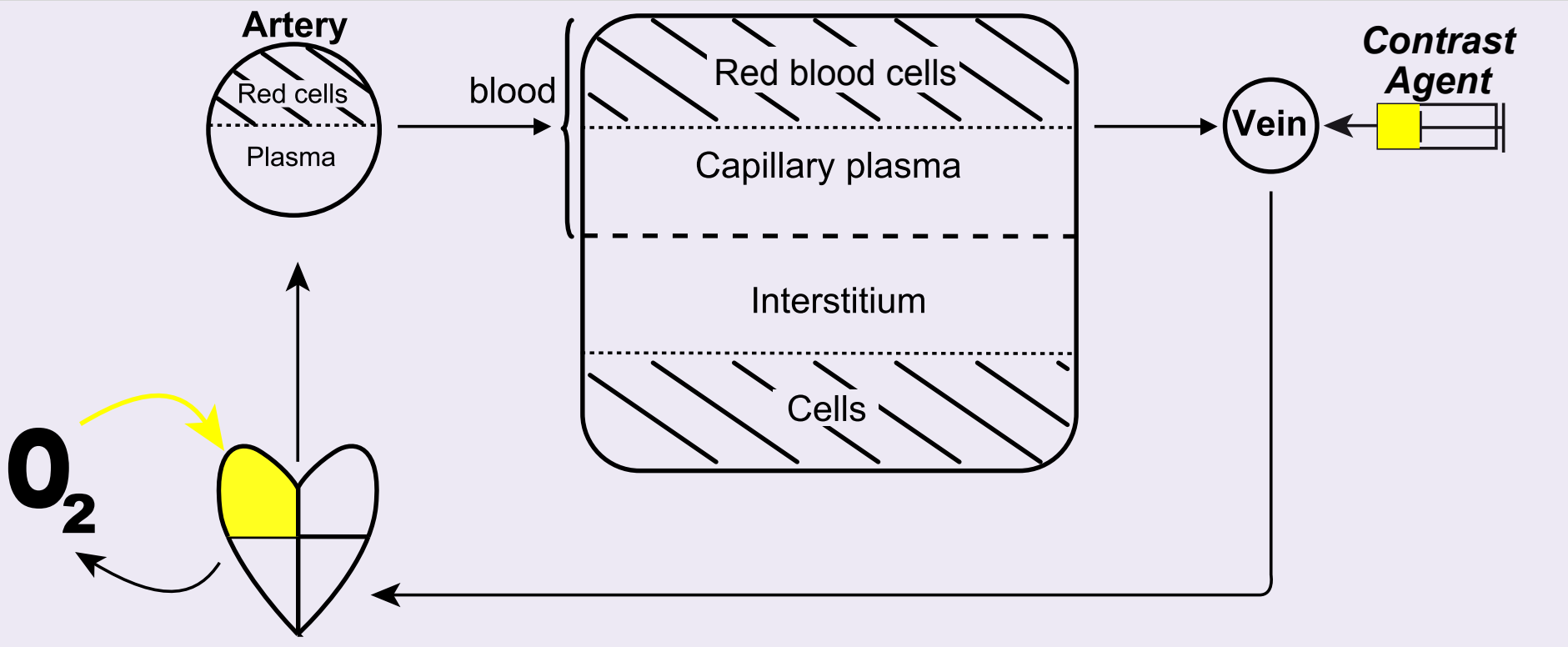
Parametric model for tissue microvascular circulation.



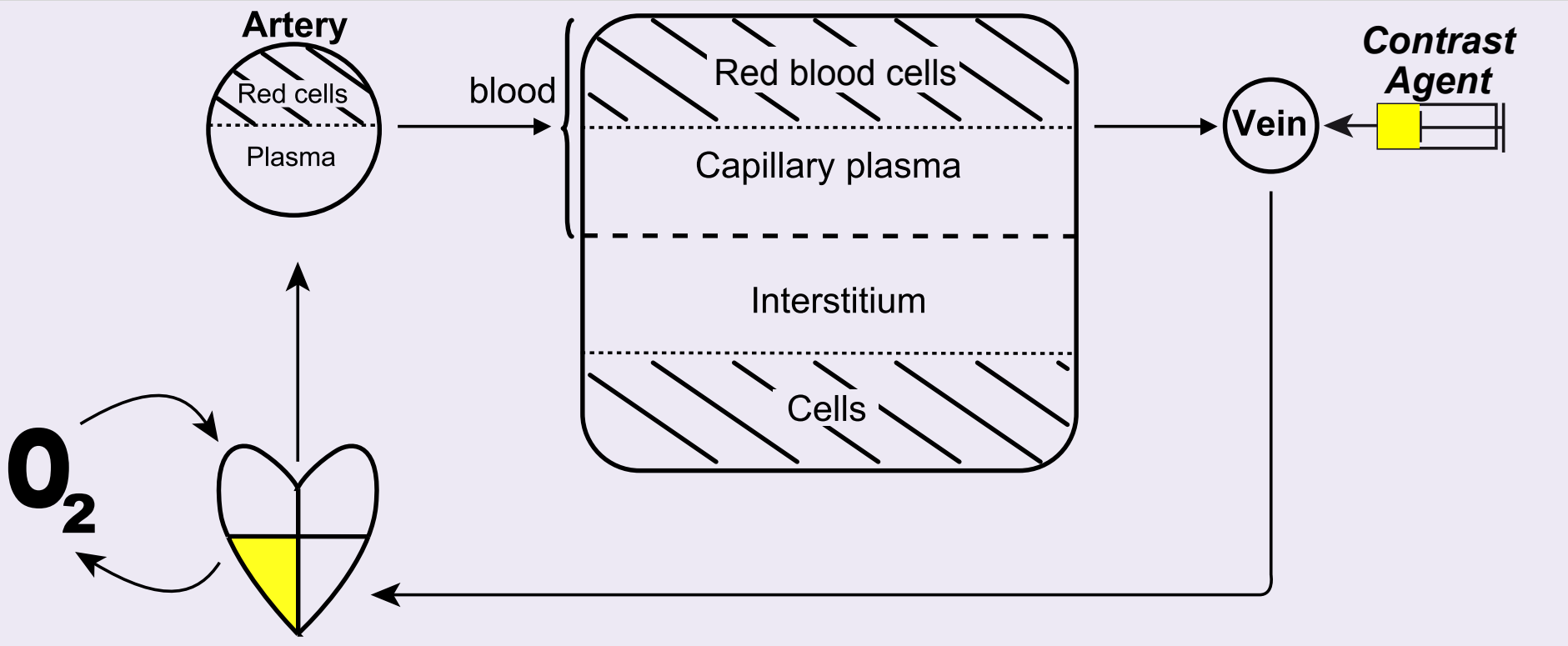
Parametric model for tissue microvascular circulation.



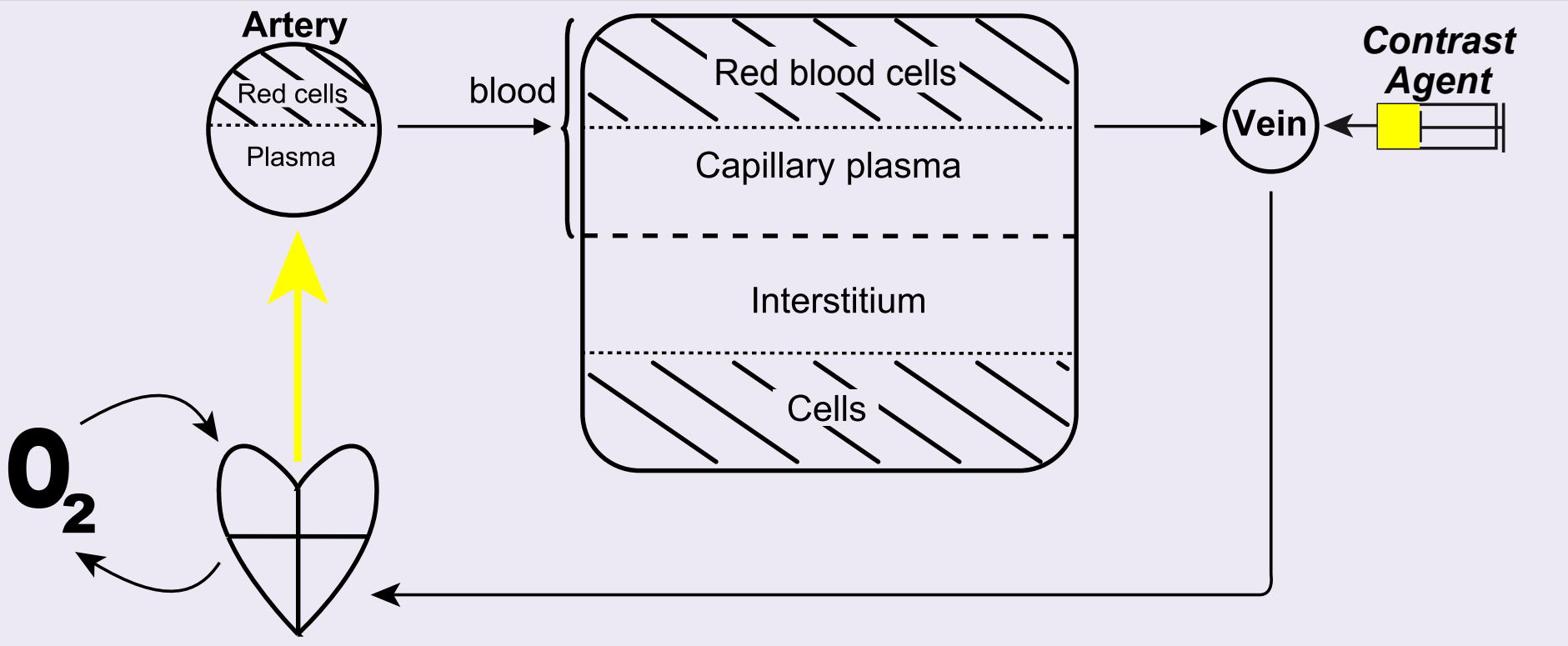
Parametric model for tissue microvascular circulation.



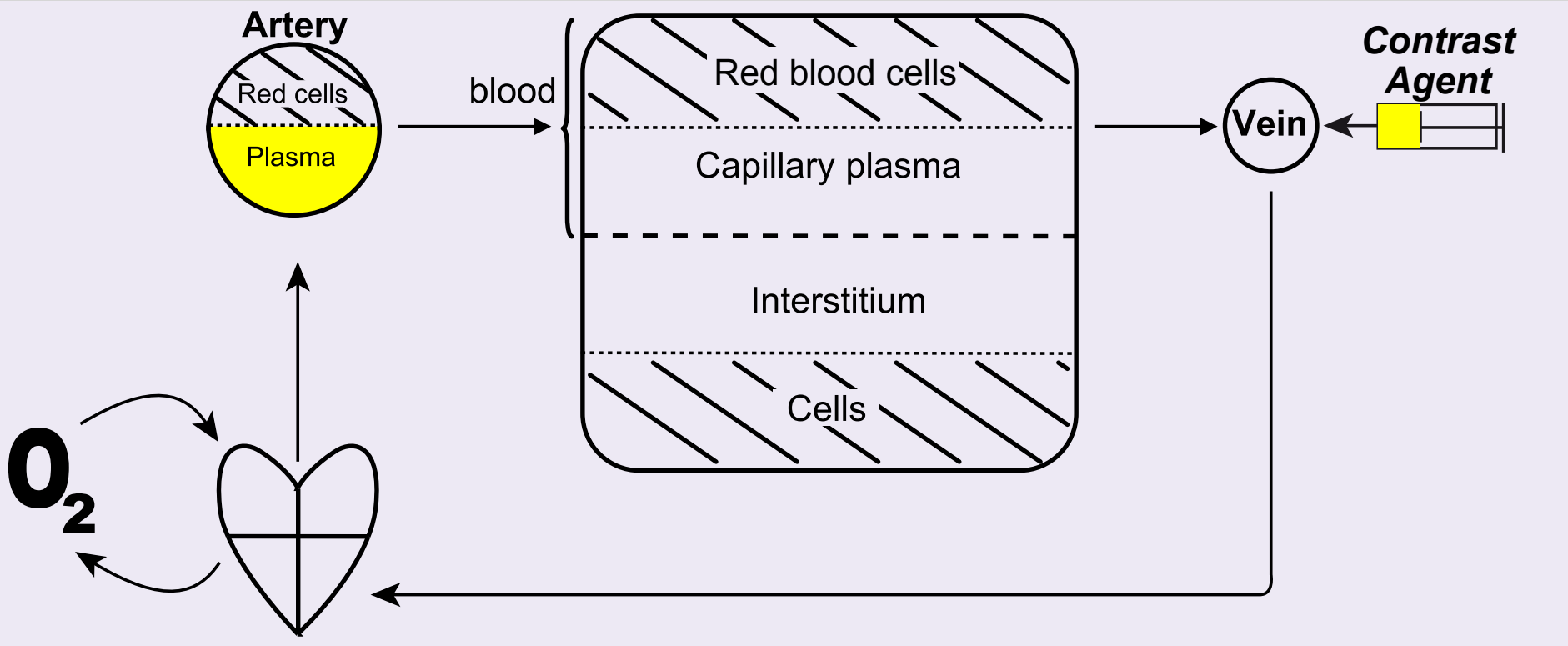
Parametric model for tissue microvascular circulation.



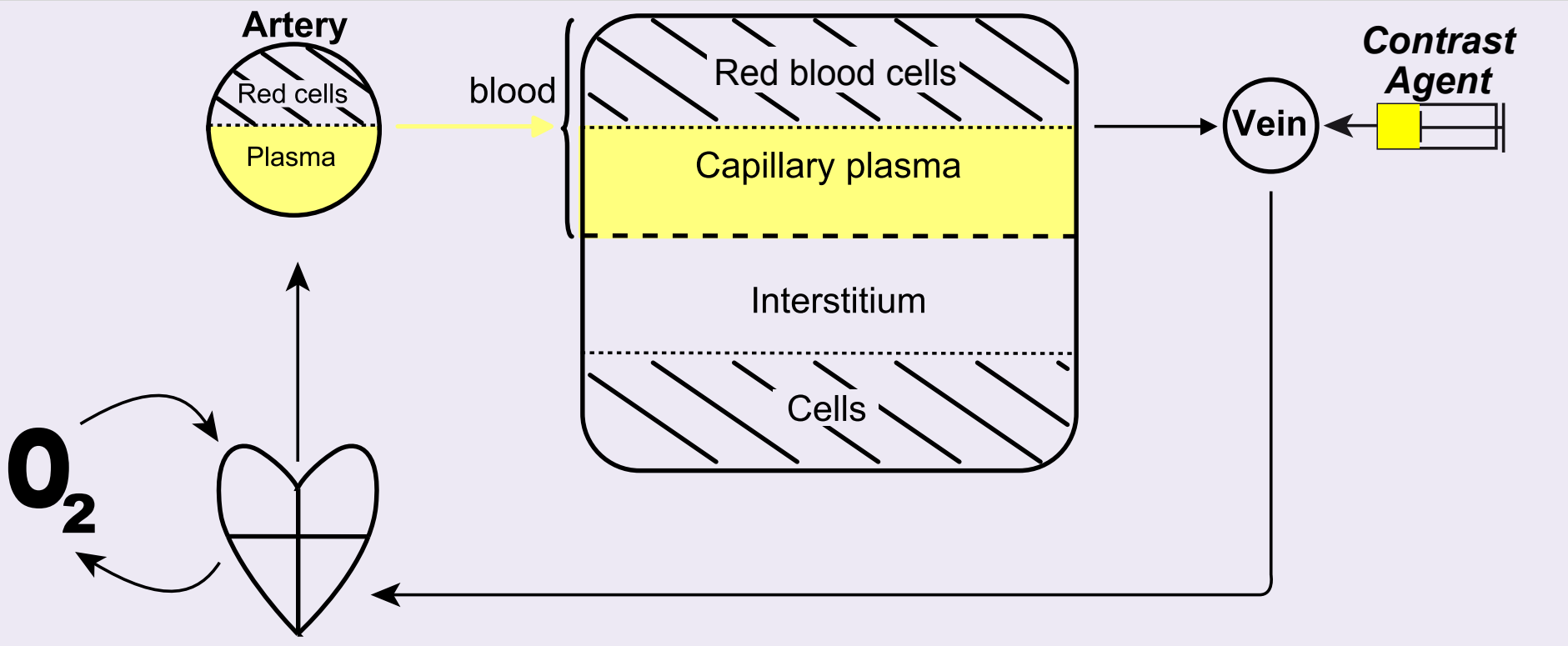
Parametric model for tissue microvascular circulation.



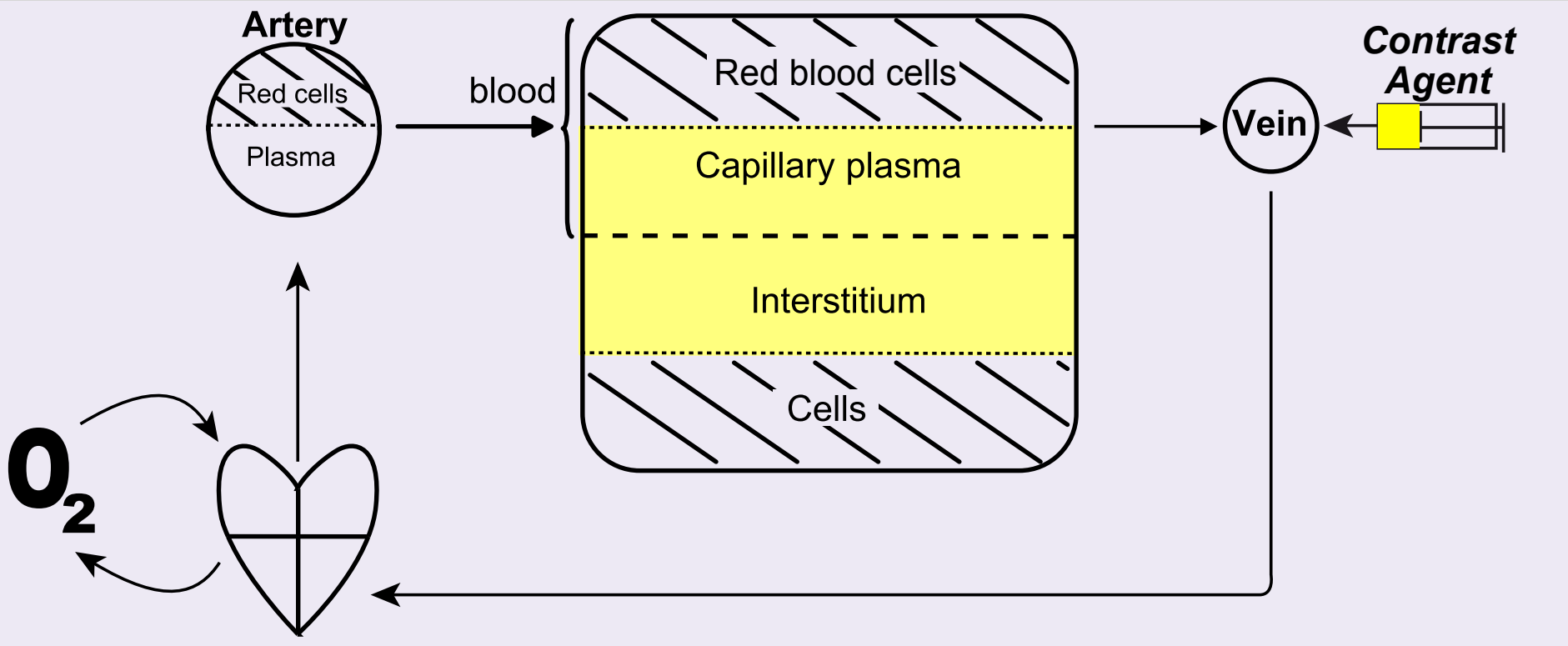
Parametric model for tissue microvascular circulation.



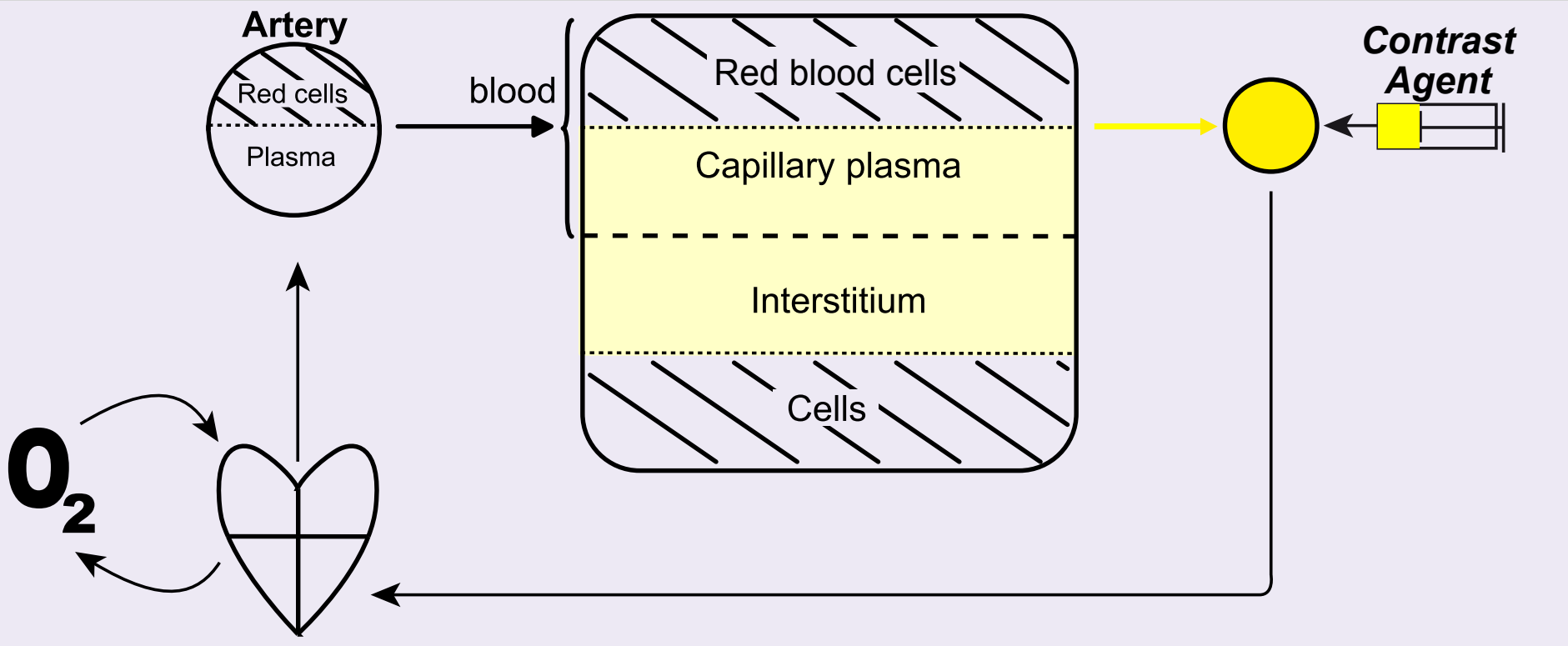
Parametric model for tissue microvascular circulation.



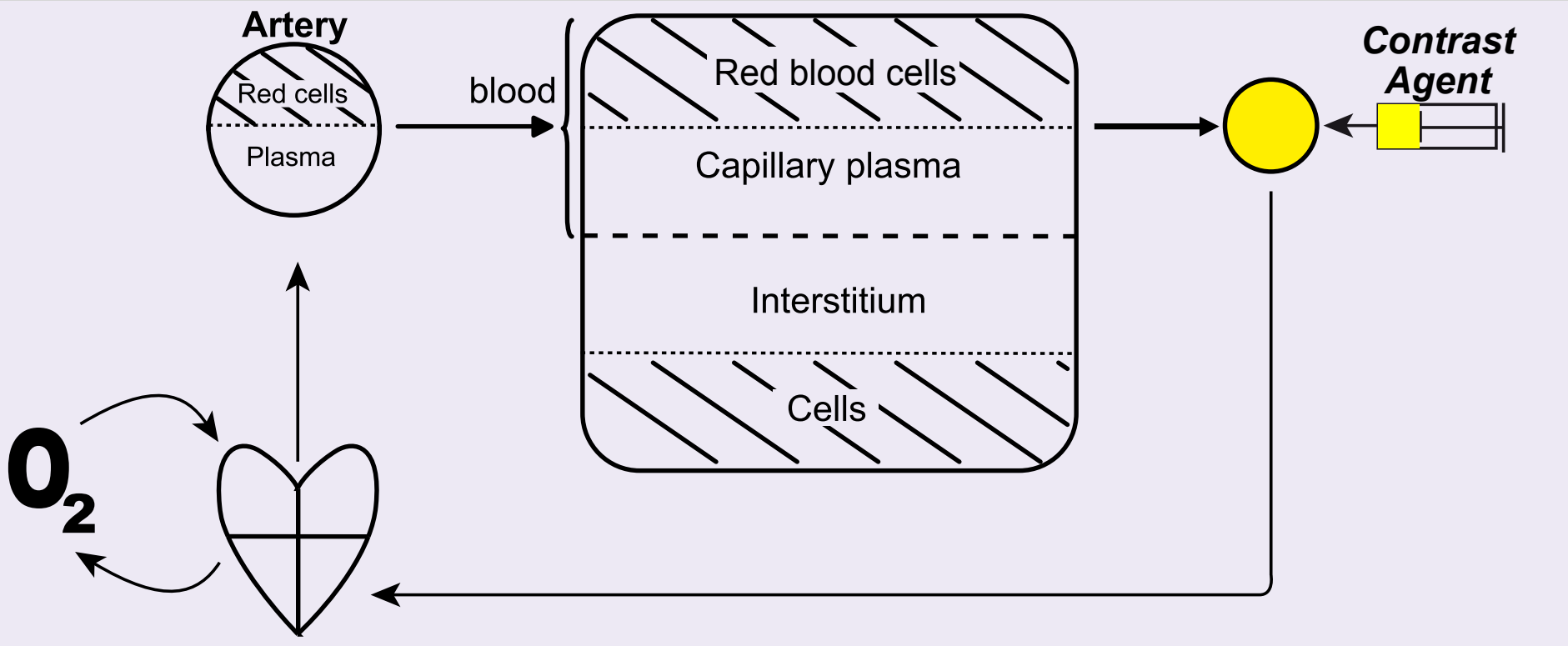
Parametric model for tissue microvascular circulation.



Parametric model for tissue microvascular circulation.

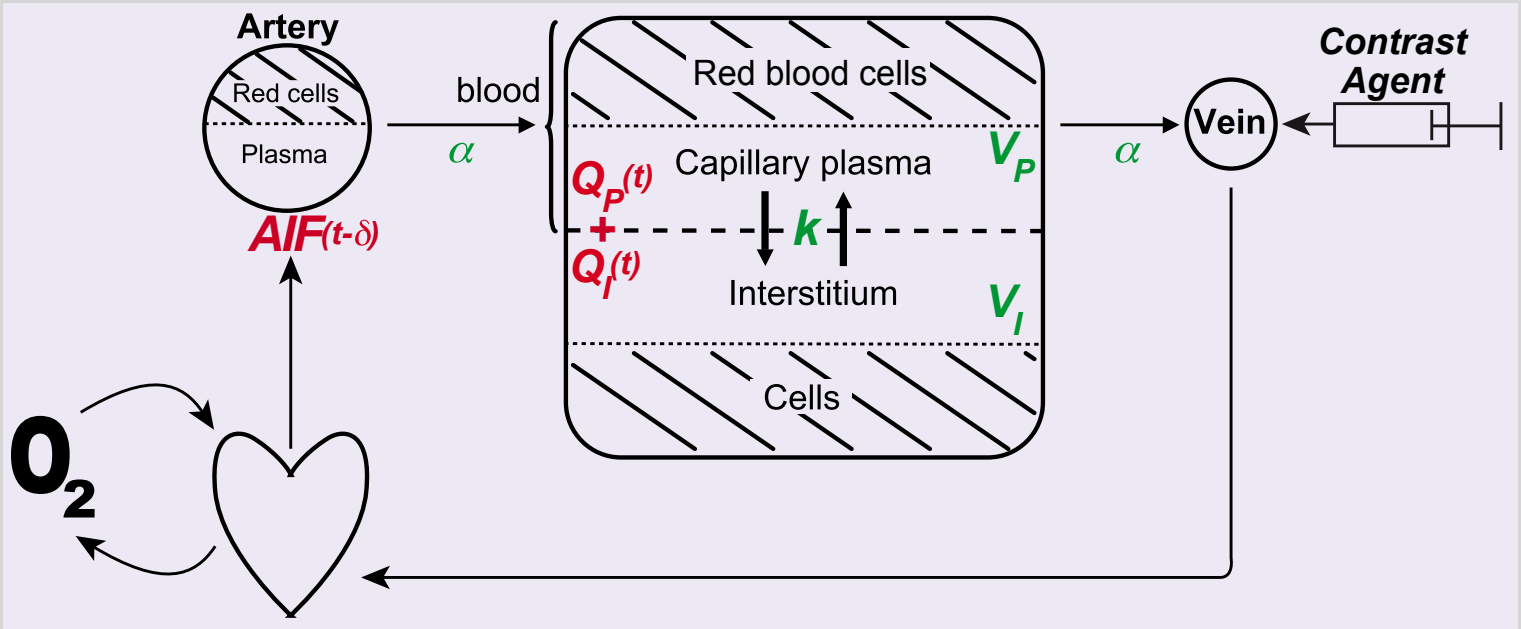


Parametric model for tissue microvascular circulation.



Parametric model for tissue microvascular circulation

with C.A. Cuénod, B. Favetto, V. Genon-Catalot, A. Samson'11.



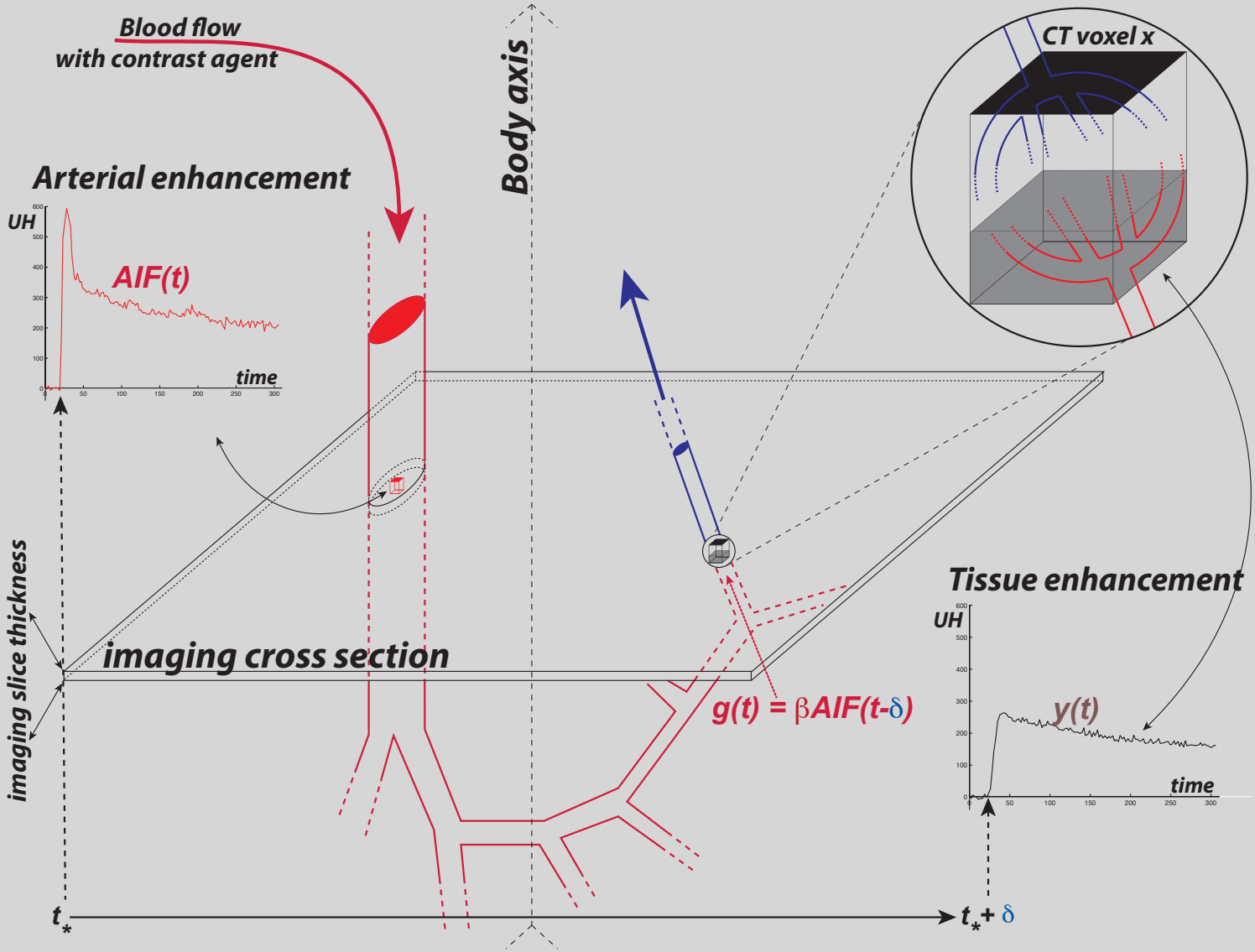
$$\begin{cases} dQ_P(t)/dt &= \frac{\alpha}{1-h} AIF(t-\delta) - \frac{k}{V_P} Q_P(t) + \frac{k}{V_I} Q_I(t) - \frac{\alpha}{V_P} Q_P(t) \\ dQ_I(t)/dt &= \frac{k}{V_P} Q_P(t) - \frac{k}{V_I} Q_I(t) \end{cases}$$

A simple vision of an inverse problem:

Given AIF and $Q = Q_P + Q_I$ noisily observed at $t_0, \ldots, t_n$:

α, k, V_I, V_P do not depend on AIF.

A non parametric complex modelization



Laplace convolution model for microvascularization

Queuing system with one entrance $\cdot/G/\infty$-type and one exit ($t \in \mathbb{R}_+$).

- $AIF(t)$ — number of arrivals in aorta voxels at time t, $AIF(0) = 0$
- $g(t) := \beta AIF(t - \delta)$ — number of arrivals in tissue voxel x at time t
- $Q(t)$ — number of particles in tissue voxel x at time t
- S_i — *i.i.d.* particle sojourn times in tissue voxel x with c.d.f. F

Link between arrivals and sojourn times:

$$\mathbb{E}Q(t) = \underbrace{\int_0^t g(\tau)\, d\tau}_{\text{arrived before time } t} - \underbrace{\int_0^t g(t-\tau) * P(S_1 \le \tau)\, d\tau}_{\text{left before time } t} = \int_0^t g(t-\tau)(1 - F(\tau))d\tau.$$

Laplace convolution model for microvascularization

Queuing system with one entrance $\cdot/G/\infty$-type and one exit ($t \in \mathbb{R}_+$).

- $AIF(t)$ — number of arrivals in aorta voxels at time t, $AIF(0) = 0$
- $g(t) := \beta AIF(t-\delta)$ — number of arrivals in tissue voxel x at time t
- $Q(t)$ — number of particles in tissue voxel x at time t
- S_i — *i.i.d.* particle sojourn times in tissue voxel x with c.d.f. F

Link between arrivals and sojourn times:

$$\mathbb{E}Q(t) = \underbrace{\int_0^t g(\tau)\,d\tau}_{\text{arrived before time } t} - \underbrace{\int_0^t g(t-\tau) * P(S_1 \le \tau)\,d\tau}_{\text{left before time } t} = \int_0^t g(t-\tau)(1-F(\tau))d\tau.$$

Discrete Laplace convolution model with noisy observations:

$$AIF(t_i) \qquad \text{and} \qquad Q(t_i) = AIF \otimes \underbrace{\beta(1-F)}_{R}(t_i - \delta) + \sigma\varepsilon_i,$$

for $i = 1, \ldots, n$ with ε_i independent and identically distributed $\mathcal{N}(0,1)$ and $0 \le t_1 \le \ldots \le t_n = T_n$.

$R := \beta(1-F)$ **unknown function to estimate** → **ill-posed pb**

Laplace deconvolution using Laguerre functions

with F. Comte, C.-A. Cuénod, M. Pensky in JRSS-B 2016

- Consider the $L_2(\mathbb{R}^+)$ orthonormal basis of the Laguerre fonctions $\phi_k(t) = e^{-t/2}L_k(t)$ for $k \in \mathbb{N}$.
- Consider the decompositions of the functions R, A et Q on this basis:

$$R(t) = \sum_{k=0}^{\infty} r_k \phi_k(t), \quad A(t) = \sum_{k=0}^{\infty} a_k \phi_k(t), \quad Q(t) = \sum_{k=0}^{\infty} Q_k \phi_k(t)$$

- Thanks to Abramovitz, Stegun (1972, 22.13.14):

$$\int_0^t \phi_k(x)\phi_j(t-x)dx = \phi_{k+j}(t) - \phi_{k+j+1}(t)$$

and we have $\boxed{Q(t_i) = \int_0^{t_i} A(s)R(t_i - s)ds + \sigma\epsilon_i} \Leftrightarrow \boxed{\vec{\mathbf{Q}}_\infty = \mathbf{A}_\infty \vec{\mathbf{R}}_\infty + \sigma\vec{\mathbf{e}}_\infty}$ with:

$$\vec{\mathbf{Q}}_\infty = \begin{pmatrix} Q_0 \\ Q_1 \\ \vdots \\ Q_m \\ \vdots \end{pmatrix}, \quad \mathbf{A}_\infty = \begin{pmatrix} a_0 & 0 & \cdots & 0 & \cdots \\ a_1 - a_0 & a_0 & \cdots & 0 & \cdots \\ \vdots & \vdots & \ddots & \vdots & \\ a_m - a_{m-1} & \vdots & \cdots & a_0 & \cdots \\ \vdots & \vdots & \cdots & \vdots & \ddots \end{pmatrix}, \quad \vec{\mathbf{R}}_\infty = \begin{pmatrix} r_0 \\ r_1 \\ \vdots \\ r_m \\ \vdots \end{pmatrix}.$$

$\Rightarrow$ Provide a <u>theoretical</u> solution $\boxed{\hat{\vec{\mathbf{R}}}_\infty = A_\infty^{-1}\vec{\mathbf{Q}}_\infty}$ . . . unfortunately not usable.

Laplace deconvolution using Laguerre functions

... going from theoretical to practical solution

Consider the truncations at size m of the previous expansions

$$\vec{\mathbf{Q}}_m = \begin{pmatrix} Q_0 \\ Q_1 \\ \vdots \\ Q_m \end{pmatrix}, \quad \mathbf{A}_m = \begin{pmatrix} a_0 & 0 & \cdots & 0 \\ a_1 - a_0 & a_0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ a_m - a_{m-1} & \vdots & \cdots & a_0 \end{pmatrix},$$

and their linear least-square estimates $\hat{\vec{\mathbf{Q}}}_m$, $\hat{\mathbf{A}}_m$ using design matrix $\Phi_m = \big(\phi_k(t_j)\big)_{1\le j\le n, 0\le k\le m}$.
Using

$$\boxed{\hat{\vec{\mathbf{R}}}_m := \hat{\mathbf{A}}_m^{-1} J_{m,M} \hat{\vec{\mathbf{Q}}}_M \quad \text{and} \quad \hat{R}_m(x) := \sum_{k=0}^{m} \hat{\vec{\mathbf{R}}}_m[k]\phi_k(x)}$$

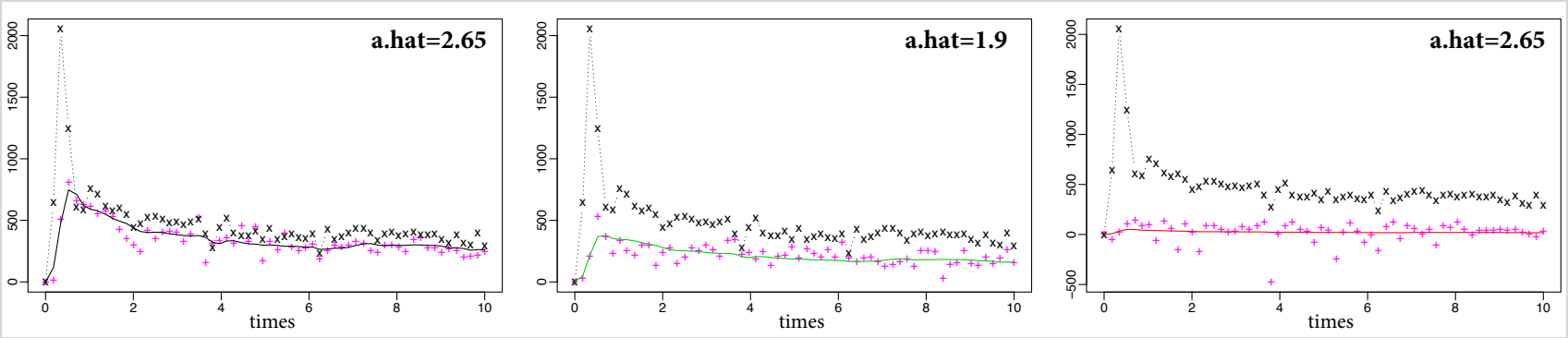
the following bias-variance decomposition of the risk holds:

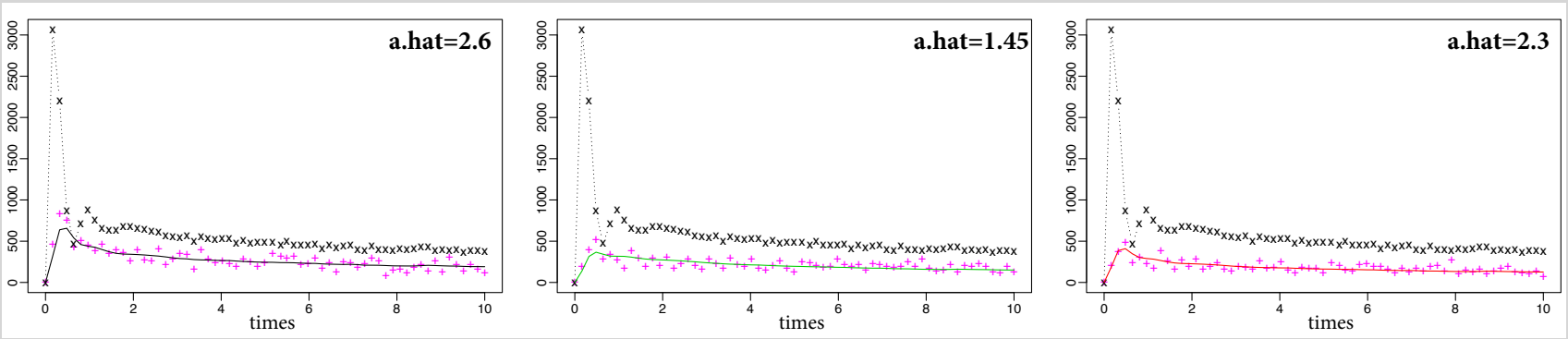
$$\boxed{\mathbb{E}(\|R - \hat{R}_m\|_2^2) \le \|R - R_m\|_2^2 + \mathrm{Tr}(\Sigma_m)\big[\sigma^2 + \frac{C}{3n}\big]}$$

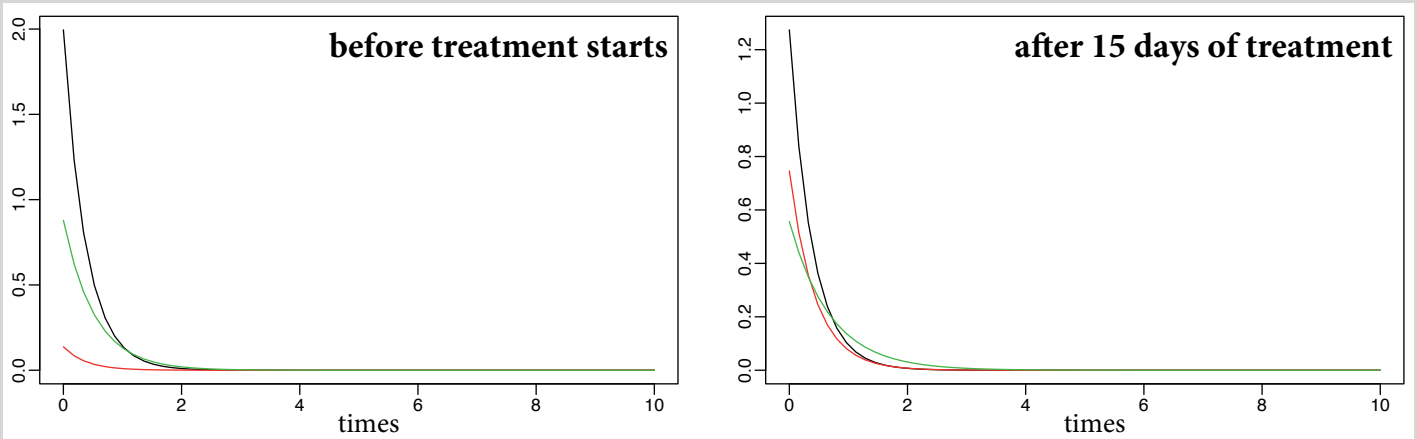
with $\Sigma_m = [(\Phi_M{}^T \Phi_M)^{-1}]_m([\mathbf{A}_M \mathbf{A}_M^T]_m)^{-1}$ and $J_{m,M} = (Id_m, O_{m,M-m})$.

Chose m using penalized least-squares

Real examples from two DCE-MRI

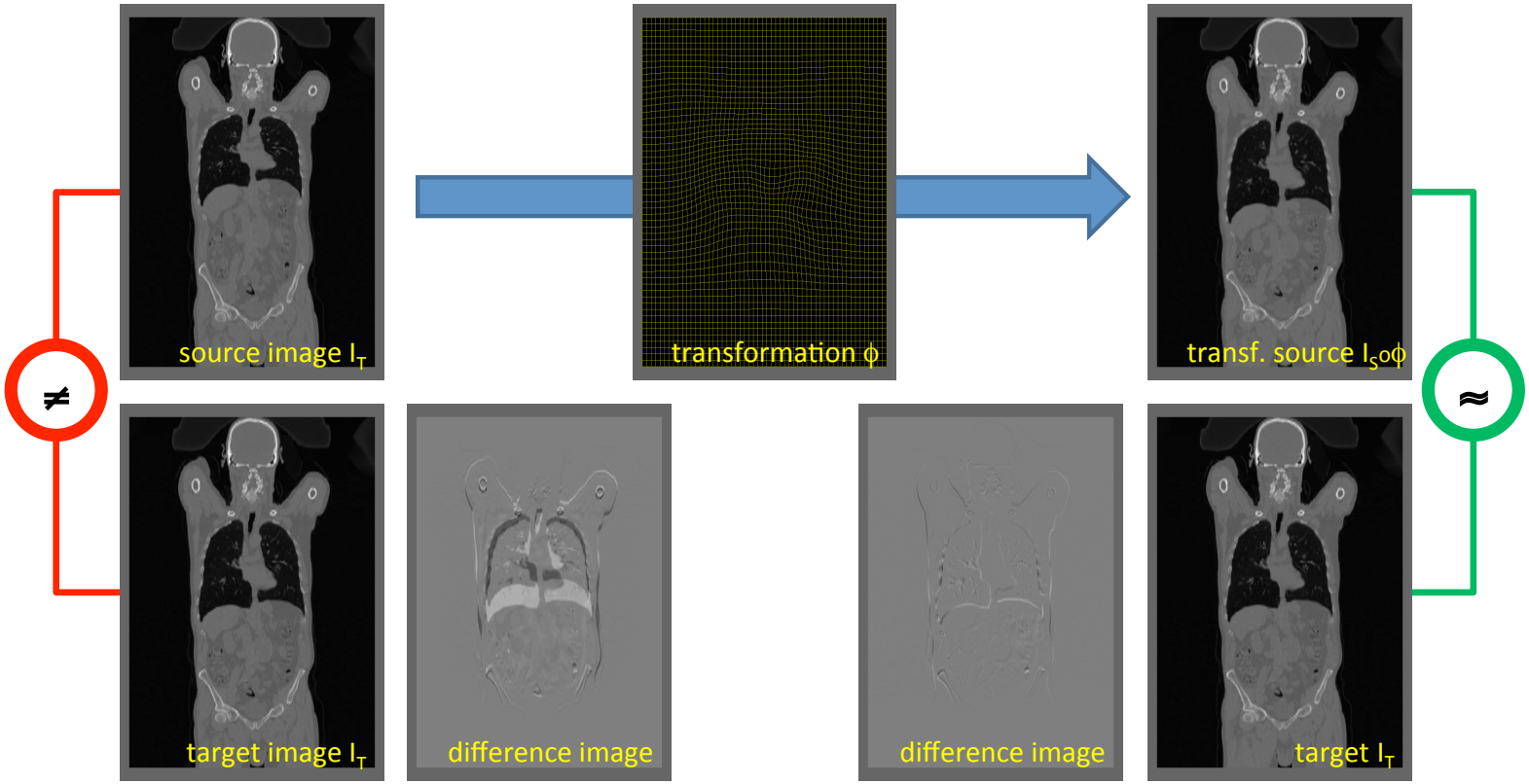






Dealing with non-rigid movements

slide from Nikos Paragios



Compute deformation ϕ, such that the transformed *source* $I_S \circ \phi$ matches *target* I_T by minimizing the image-based difference measure E_D.

Dealing with non-rigid movements

slide from Nikos Paragios

Intensity-based Deformable Registration as Energy Minimization

$$\phi' = \arg\min_{\phi} \left[E_{\mathrm{D}}(I_{\mathrm{S}} \circ \phi, I_{\mathrm{T}}) + \lambda E_{\mathrm{R}}(\phi) \right]$$

$\phi : \mathbb{R}^d \to \mathbb{R}^d$

$I : \mathbb{R}^d \to \mathbb{R}$

Transformation ϕ
can assumed as element of:

- Can be modeled as elemet of a Hilbert space (L^2, Sobolev space) or group/manifold (group of diffeomorphisms)
- Has to be parametrized for digital representation (B-Spline FFDs, DCT, RBFs)

Difference Measure between:

- Target image I_T
- Warped source image $I_S \circ \phi$

Examples:

- Sum of squared differences (SSD)
- Sum of absolute differences (SAD)
- Correlation Coefficient (CC)
- Correlation Ratio (CR)
- Mutual Information (MI)

Regularization term:

- Models the behaviour of underlying elastic model (internal energy)
- Incorporates prior knowledge
- can be required to constrain problem

Examples:

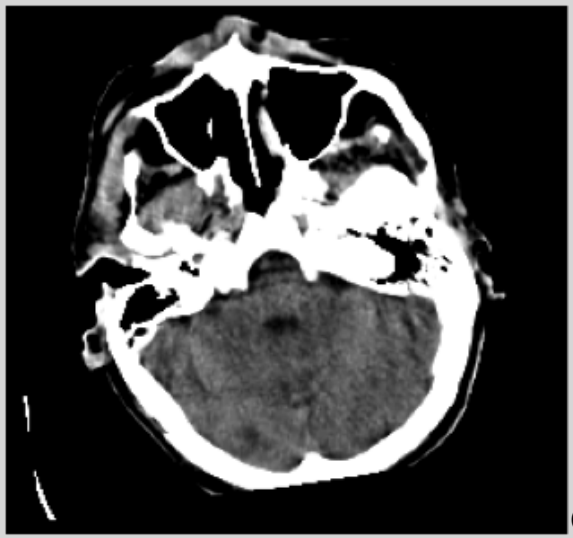
- Diffusion (1st-order) ((in-)homogeneous, (an-)isotropic)
- Curvature/Bend. Energy (2nd-order)
- Linear Elasticity

Dealing with non-rigid movements

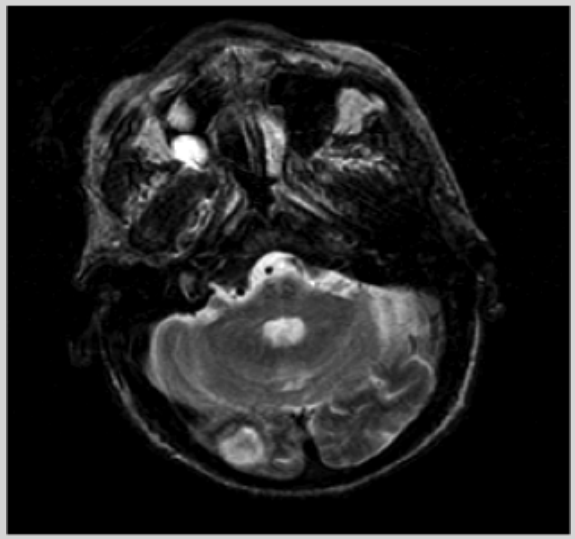
figure from Nikos Paragios

A complex but reasonable problem for corresponding intensities

A more complex but still reasonable problem for multi-modalities



CT $\Longleftrightarrow$ MRI



Need to

- infer one modality from the other one
- apply sophisticated similarity measures

!!! HOWEVER IMPOSSIBLE WHEN GRAY LEVELS CHANGE DYNAMICALLY !!!

Take home message

Tools to build good DCE imaging biomarkers are available.

Tools to solve noise and movement issues are available.

However each previous tool fails separately.

PROBLEMS ARE DEEPLY INTERMINGLED:

- Feature extraction needs registration.
- Registration requires similarity measure between dynamics.
- Without deconvolution dynamics change with AIF.
- Deconvolution requires registration.

Dictionary for integrated registration and labeling

going from not so large to complex problem

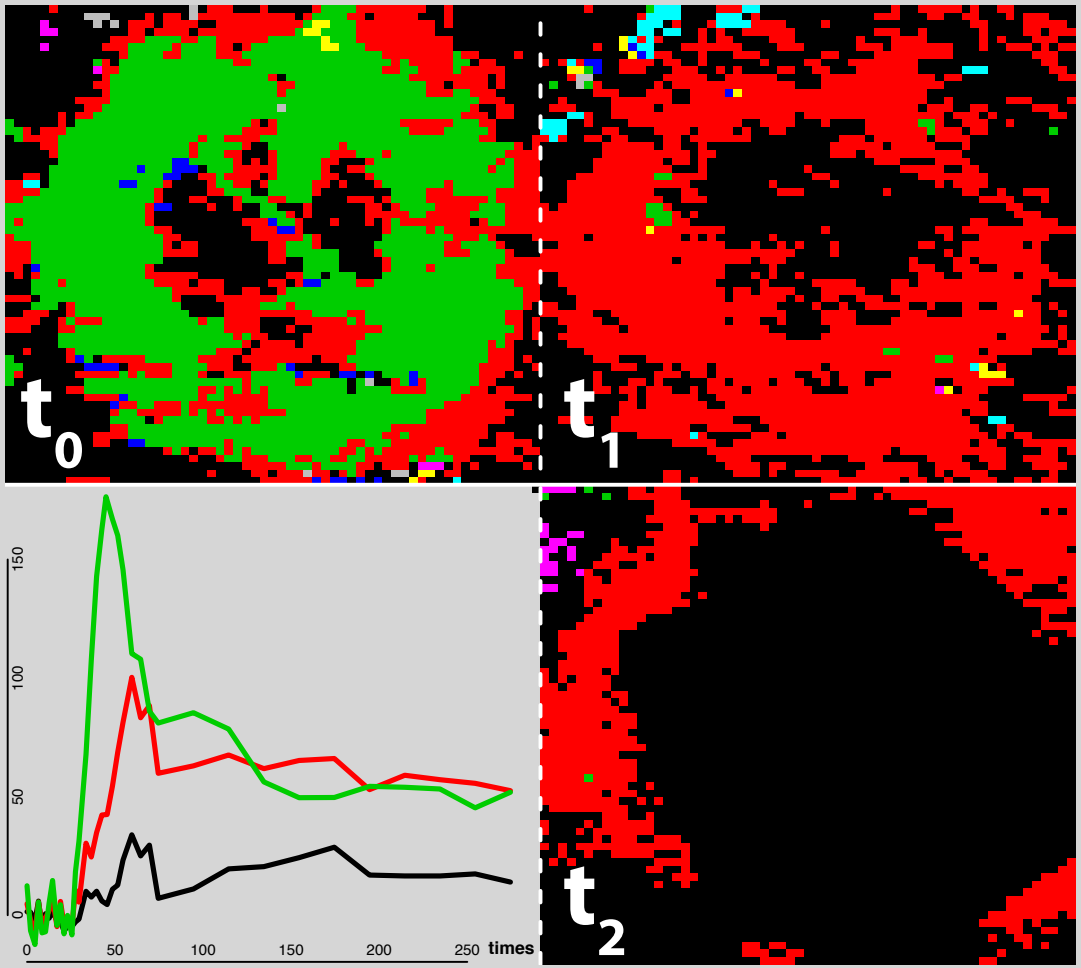
- **Grade DCE sequences from low to high motion.**
- **Clusterize low motion DCE sequences and retrieve denoised cluster dynamics.**
- **Deconvole cluster dynamics with respect to AIF to get reproducible parameters of the microcirculation.**
- **Reduce the set of all reproducible parameters to build a smaller dictionary D.** (using mixture models, unsupervised classification, etc)
- **For a DCE sequence showing movements**
  - Find AIF (easy),
  - Realize $AIF \otimes D$ to get a personalized dictionary of enhancement D_{AIF},
  - Use D_{AIF} as input of the AIF-adapted similarity measure
- **Improve D with registered DCE sequences iteratively.**

When D is optimized, registration of new DCE sequence provides an association "voxel to microcirculation parameter" !!!

D can be large if hierarchical : ensure small registration cost at each level of the hierarchy.

Direct clustering between DCE as follow-up biomarkers

Example - Responder

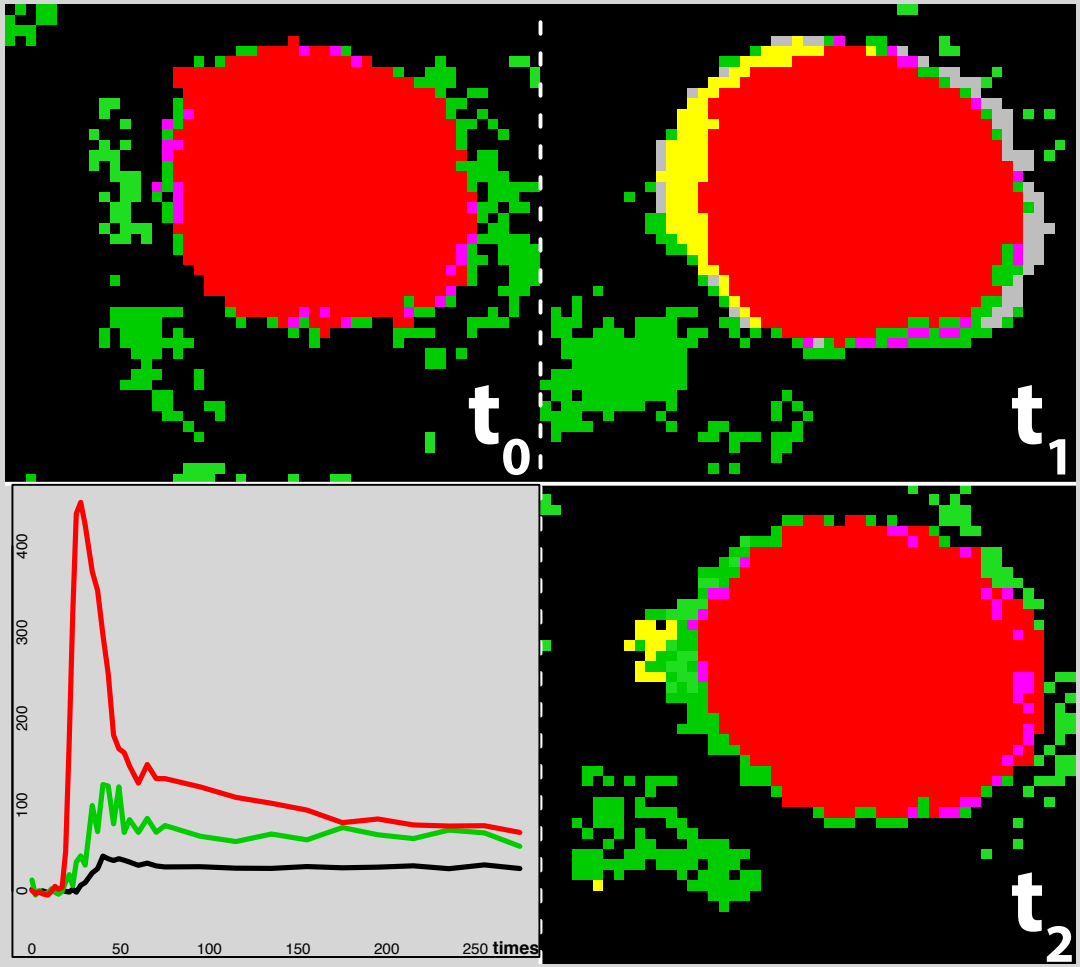


Follow-up and propective Biomarker in cancer treatment

t_0: Before treatment — t_1: 1 week — t_2: 3 months

Direct clustering between DCE as follow-up biomarkers

Example - Not Responder



Follow-up and propective Biomarker in cancer treatment

t_0: Before treatment — t_1: 1 week — t_2: 3 months

Direct dynamical image clustering: is that OK?

Is the direct comparison as good as an indirect one ?

Model :	$Q^x(t_i) = q^x(t_i) + \sigma\varepsilon_i^x,\ i = 1 \dots n,$	**Image made of time-series**
Tools :	$H_0^{xy} : q^x - q^y \equiv 0,$	**Direct test of nullity**

Direct dynamical image clustering: is that OK?

Is the direct comparison as good as an indirect one ?

Model : $Q^x(t_i) = q^x(t_i) + \sigma\varepsilon_i^x,\ i = 1 \dots n,$ **Image made of time-series**

Tools : $H_0^{xy} : q^x - q^y \equiv 0,$ **Direct test of nullity**

HOWEVER

Discrete Laplace convolution model with noisy observations:

$$AIF(t_i) \qquad \text{and} \qquad Q(t_i) = AIF \otimes \underbrace{\beta(1-F)}_{R}(t_i - \delta) + \sigma\varepsilon_i,$$

for $i = 1, \dots, n$ with ε_i independent and identically distributed $\mathcal{N}(0,1)$ and $0 \le t_1 \le \dots \le t_n = T_n$.

Should we prefer an indirect test for $H_0^{xy} : R^x - R^y \equiv 0$???

Direct dynamical image clustering: is that OK?

Is the direct comparison as good as an indirect one ?

ELSEVIER

Journal of Statistical Planning and Inference

Volume 141, Issue 5, May 2011, Pages 1849–1861

Testing inverse problems: A direct or an indirect problem?

B. Laurent, J.-M. Loubes, C. Marteau

Direct dynamical image clustering: is that OK?

Is the direct comparison as good as an indirect one ?

ELSEVIER

Journal of Statistical Planning and Inference

Volume 141, Issue 5, May 2011, Pages 1849–1861

Testing inverse problems: A direct or an indirect problem?

B. Laurent, J.-M. Loubes, C. Marteau

Theorem 3.1 *Let $(Y_j)_{j\geq 1}$ a sequence obeying to model (3). Let $\alpha, \beta \in (0,1)$ be fixed. Let $\mathcal{E}^{\mathcal{X}}_{a,2}(R)$ the ellipsoid defined in (4). We assume that $0 < \sigma < 1$. Then, in the four cases displayed in Table 1, we have*

- *Every level-α test minimax for H_0^{DP} on $\mathcal{E}^{\mathcal{Y}}_{c,2}(R)$ is also minimax for H_0^{IP} on $\mathcal{E}^{\mathcal{X}}_{a,2}(R)$,*
- *There exist level-α tests minimax for H_0^{IP} on $\mathcal{E}^{\mathcal{X}}_{a,2}(R)$ but not for H_0^{DP} on $\mathcal{E}^{\mathcal{Y}}_{c,2}(R)$,*

where for all $k \geq 1$, $c_k = a_k b_k^{-1}$.

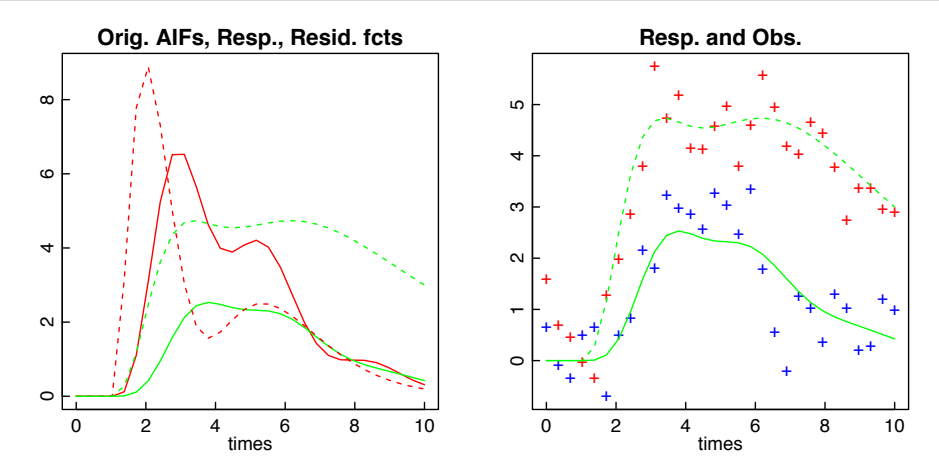
Note that under ellipsoid constraint, previous results hold both for mildly and severely ill-posed problems. Hence the conclusion of this theorem is that testing in the space of observations should be preferred rather than building specific tests designed for inverse problem which will not improve the rates and will introduce additional difficulties.

Direct clustering between DCE images: Is that possible ?

How to deal with the non reproducibility of the kernel ?

DCE images don't have the same AIF (convolution kernel) !

How to realize direct comparison i.e. without deconvolution ?



Cross-testing in Laplace convolutions

with R. Castro and I. Dattner

We observe

$$\left.\begin{array}{l} Q_j(t_i) = q_j(t_i) + \sigma_j \varepsilon_j, \\ A_j(t_i) = a_j(t_i) + \tau_j \nu_j, \end{array}\right\} \quad \text{for } i = 1, \ldots, n.$$

with $q_j = a_j \otimes R_j$, for two DCE sequences indexed by $j = 1, 2$.

We aim at testing $H_0 : R_1 = R_2$ versus $H_1 : R_1 \neq R_2$

Classical approach Step 1: **Deconvolution** to get $\hat{R}_1$ and $\hat{R}_2$; Step 2: **Comparison** of $\hat{R}_1$ and $\hat{R}_2$.

HOWEVER direct comparison avoids ill-posedness difficulties and should be preferred.

Cross-testing in Laplace convolutions

with R. Castro and I. Dattner

We observe

$$\left.\begin{array}{l} Q_j(t_i) = q_j(t_i) + \sigma_j \varepsilon_j, \\ A_j(t_i) = a_j(t_i) + \tau_j \nu_j, \end{array}\right\} \quad \text{for } i = 1, \ldots, n.$$

with $q_j = a_j \otimes R_j$, for two DCE sequences indexed by $j = 1, 2$.

We aim at testing $H_0 : R_1 = R_2$ versus $H_1 : R_1 \neq R_2$

Classical approach Step 1: **Deconvolution** to get $\hat{R}_1$ and $\hat{R}_2$; Step 2: **Comparison** of $\hat{R}_1$ and $\hat{R}_2$.

HOWEVER direct comparison avoids ill-posedness difficulties and should be preferred.

IDEA for direct comparison in between sequences:

$$a_1 \otimes q_2 - a_2 \otimes q_1 = a_1 \otimes a_2 \otimes R_2 - a_2 \otimes a_1 \otimes R_1 = a_1 \otimes a_2 \otimes (R_2 - R_1).$$

Thanks to associative and commutative properties of Laplace convolution!

Cross-testing in Laplace convolution models: statistic

We observe

$$\left.\begin{array}{l} Q_j(t_i) = q_j(t_i) + \sigma_j \varepsilon_j, \\ A_j(t_i) = a_j(t_i) + \tau_j \nu_j, \end{array}\right\} \quad \text{for } i = 1, \ldots, n.$$

with $q_j = a_j \otimes R_j$, for for two DCE sequences indexed by $j = 1, 2$.

Given some projection estimators $\tilde{a}_j$ of a_j and $\tilde{q}_j$ of q_j, for $j = 1, 2$, we consider

$$\begin{aligned} \tilde{h}: \quad &= \tilde{a}_1 \otimes \tilde{q}_2 - \tilde{a}_2 \otimes \tilde{q}_1 \\ &= a_1 \otimes q_2 - a_2 \otimes q_1 && \mathbf{a_1 \otimes a_2 \otimes (R_2 - R_1)} \\ &\quad + \tilde{a}_1 \otimes (\bar{q}_2 - q_2) - \tilde{a}_2 \otimes (\bar{q}_1 - q_1) + (\bar{a}_1 - a_1) \otimes q_2 - (\bar{a}_2 - a_2) \otimes q_1 && \textbf{bias} \\ &\quad + \tilde{a}_1 \otimes (\tilde{q}_2 - \bar{q}_2) - \tilde{a}_2 \otimes (\tilde{q}_1 - \bar{q}_1) && \textbf{stochastic error} \end{aligned}$$

where $\bar{f}$ denotes the projection of f.