# Numerical approximation of coupled PDEs with high dimensionality gap

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Advanced numerical methods:
Recent developments, analysis and applications
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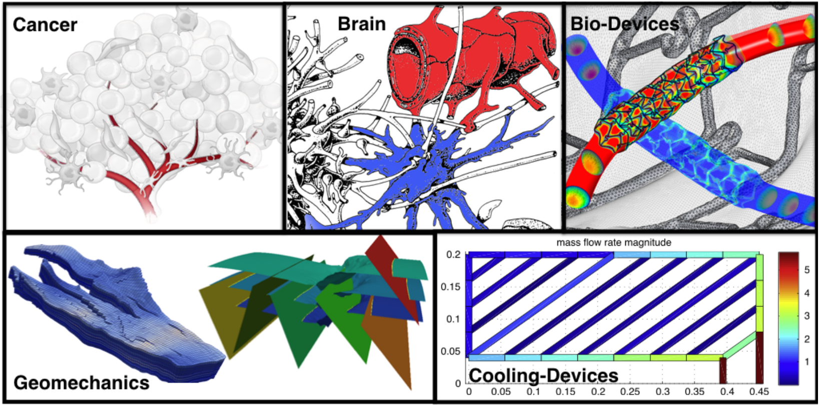
# Applications

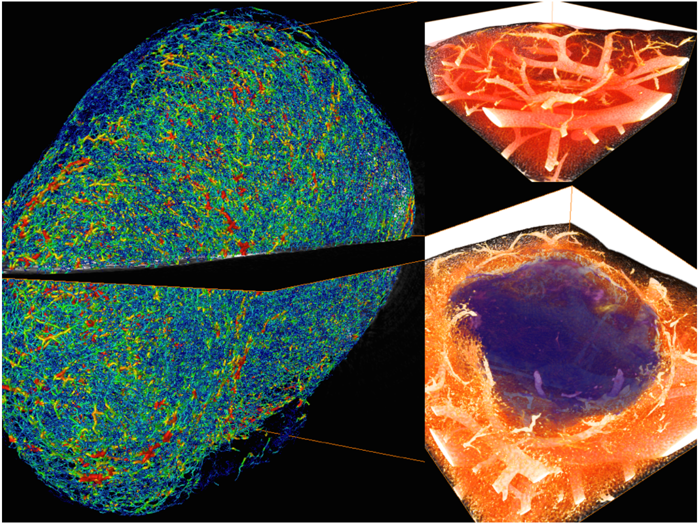
**Life sciences:** cancer, brain, biomedical devices ...




**Technology:** fracking, electronics ...

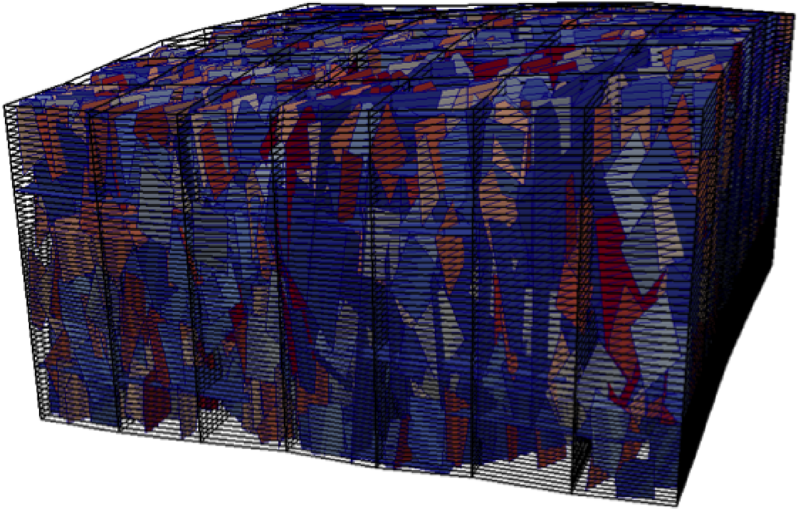
# Computational challenges: domains of complex shape

**Imaging:** 3D rendering of **blood vessels** inside a human colorectal carcinoma model, 0.5cm in diameter, using optical projection tomography (OPT). Coutesy of Simon Walker-Samuel, UCL.



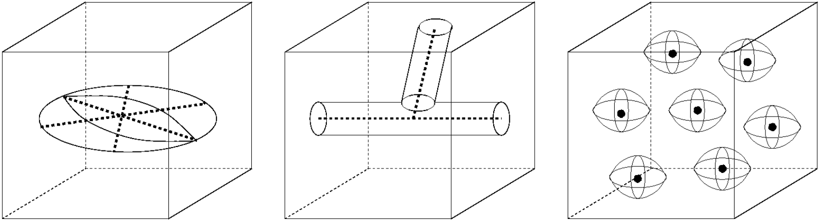
# Computational challenges: domains of complex shape

**Fracture networks:**



# Objective: a unified framework

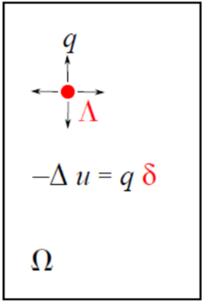
**A unified view:**



interfaces **3D-2D** channels **3D-1D** inclusions (cells, particles) **3D-0D**

**Objective:** solve coupled PDEs on **embedded manifolds** with **high dimensionality gap;**

# Mathematical chellenges: a prototype problem




**What are the main issues?**

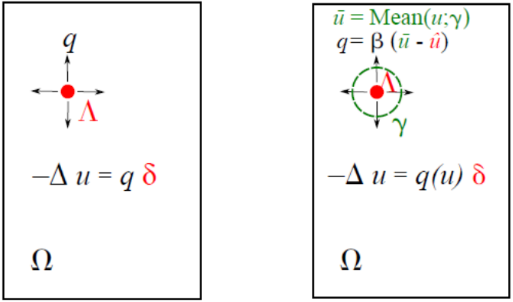
**Solution:**

$$
\begin{aligned}
u &\simeq ln(r) \\
\nabla u &\simeq \frac{1}{r} \notin L^2(\Omega)
\end{aligned}
$$

- **Simple** Poisson problem with Dirac source;

Adapted from D'Angelo C, Quarteroni A. On the coupling of 1D and 3D diffusion-reaction equations. Application to tissue perfusion problems. *Math. Models Methods Appl. Sci.* 2008.

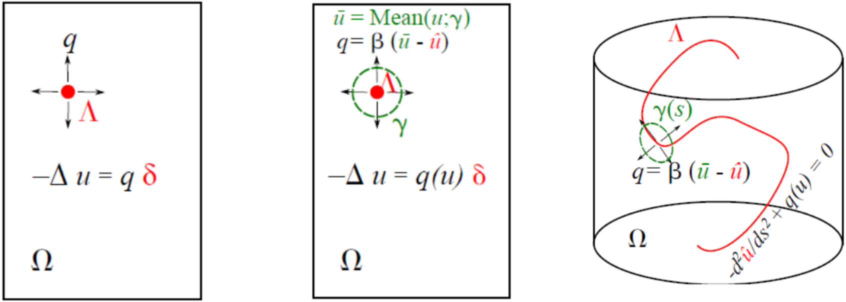
# Mathematical chellenges: a prototype problem




- **Coupled** Poisson problem with Dirac source;
- Solution-dependent flux $q$
- $q(u(x_\Lambda))$ is not admissible $\longrightarrow$ use $q(\overline{u})$

Adapted from D'Angelo C, Quarteroni A. On the coupling of 1D and 3D diffusion-reaction equations. Application to tissue perfusion problems. *Math. Models Methods Appl. Sci.* 2008.

# Mathematical chellenges: a prototype problem

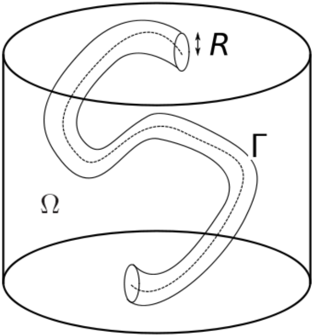



- **Coupled** Poisson problem with Dirac source;
- 3D-1D model coupling;

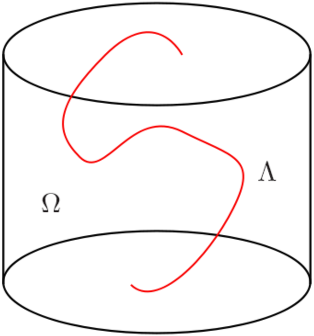
Adapted from D'Angelo C, Quarteroni A. On the coupling of 1D and 3D diffusion-reaction equations. Application to tissue perfusion problems. *Math. Models Methods Appl. Sci.* 2008.

# An example: 3D-1D description of microcirculation

from 3-dimensional models in $\mathbb{R}^3$

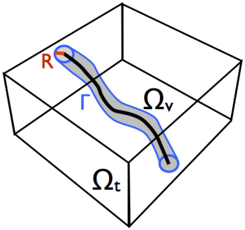



to 1-dimensional models in $\mathbb{R}^3$



# An example: governing equations of microcirculation

**Coupled flow**

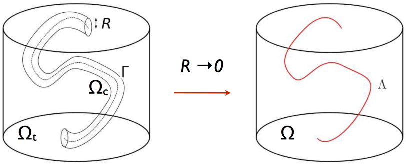



$$
\begin{cases}
\mathbf{u}_t = -\dfrac{k}{\mu}\nabla p_t & \text{in } \Omega_t \\
\nabla \cdot \mathbf{u}_t = \overbrace{-L_p^{LF}\frac{S}{V}(p_t - p_L)}^{\text{lymphatic drainage}} & \text{in } \Omega_t. \\
\rho\left(\dfrac{\partial \mathbf{u}_v}{\partial t} + (\mathbf{u}_v\cdot\nabla)\mathbf{u}_v\right) = \nabla\cdot\mathbf{T}(p_v,\mathbf{u}_v) & \text{in } \Omega_v \\
\nabla\cdot\mathbf{u}_v = 0 & \text{in } \Omega_v. \\
\mathbf{u}_v\cdot\mathbf{n} = \mathbf{u}_t\cdot\mathbf{n} = \overbrace{L_p(p_v - p_t)}^{\text{leakage}} & \text{on } \Gamma
\end{cases}
$$

Baxter, Laurence T. and Jain, Rakesh K., *Transport of fluid and macromolecules in tumor. II. Role of heterogenous perfusion and lymphatics.* Microvascular research, 1990.

# An example: embedded multiscale method

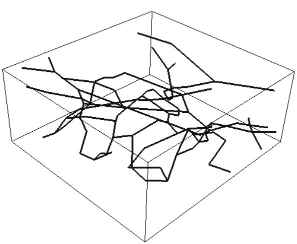
**Embedded multiscale**
= Geometric Multiscale
+ Immersed Boundary

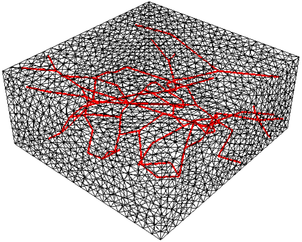



$$
\begin{cases}
-\nabla \cdot \left( \dfrac{k}{\mu} \nabla p_t \right) = L_p(\overline{p}_v - \overline{p}_t)\delta_\Lambda, \\[2ex]
-\dfrac{\pi R^4}{8\mu} \dfrac{\partial^2 \overline{p}_v}{\partial s^2} = -L_p(\overline{p}_v - \overline{p}_t)
\end{cases}
$$

**Interface conditions are replaced by concentrated sources:**

- **low computational cost;**
- **independent computational meshes of volume and network;**



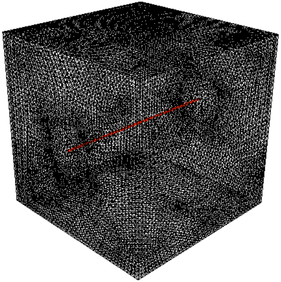


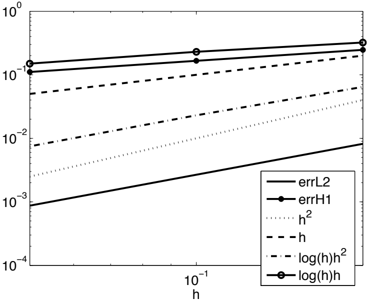
# Analysis: a-priori error estimates

1. **T. Koeppl and B. Wohlmuth.** Optimal a priori error estimates for an elliptic problem with Dirac right-hand side. SINUM, 52(4), 1753–1769; **A.H. Schatz and L.B. Wahlbin**, Interior maximum norm estimates for finite element methods, Math. Comp., 31 (1977), pp. 414–442.
2. **D'Angelo**, C. Finite element approximation of elliptic problems with dirac measure terms in weighted spaces: Applications to one- and three-dimensional coupled problems (2012) SINUM, 50 (1), pp. 194-215; **T. Apel, O. Benedix, D. Sirch, and B. Vexler**, A Priori Mesh Grading for an Elliptic Problem with Dirac Right-Hand Side, (2011) SINUM 49(3), 992-1005.

*Let $p_t \in W_0^{1,p}$ be the weak solution of the perfusion model and let $p_t^h \in V_t^h$ be the finite element approximation. The following $L^2$-error bound holds true:*

$$\|p_t - p_t^h\|_{L^2(\Omega\setminus\Omega_v)} \lesssim h^2|\log h|.$$





# A new method: set up

**Model reduction strategy:**

(i) identify the domain $\Omega_p$ with the entire $\Omega$;

(ii) decompose $v|_{\Gamma_i} = \overline{v}_{\Gamma_i} + \widetilde{v}_{\Gamma_i}$ and assume that the fluctuations $\widetilde{v}_{\Gamma_i}$ are small;

**A new reduced model:**

$$(\nabla u, \nabla v)_\Omega + \sum_{i=1}^{N} \kappa_i \overline{u}^{(i)} \overline{v}^{(i)} = \sum_{i=1}^{N} |\Gamma_i| \kappa_i U_i \overline{v}^{(i)}, \quad \forall v \in V,$$

- **A new version of the *embedded multiscale method*;**
- **It preserves all the good properties of the original problem;**
- **It features a similar algorithmic complexity of the previous version;**

# A new method: analysis

**The new reduced model:**

$$(\nabla u, \nabla v)_\Omega + \sum_{i=1}^{N} \kappa_i \overline{u}^{(i)} \overline{v}^{(i)} = \sum_{i=1}^{N} |\Gamma_i| \kappa_i U_i \overline{v}^{(i)}, \quad \forall v \in V,$$

- For $V = H_0^1(\Omega)$, There exists a unique solution $u \in H_0^1(\Omega)$ of the problem.
- Let $u$ be the weak solution and let $u_h$ be its $\mathbb{P}^1$-FEM approximation. The following estimates hold true for any $\epsilon > 0$:

$$\|u - u_h\|_{H^1(\Omega)} \lesssim h^{\frac{1}{2}-\epsilon} \|u\|_{H^{\frac{3}{2}-\epsilon}(\Omega)} \text{ and } \|u - u_h\|_{L^2(\Omega)} \lesssim h^{\frac{3}{2}-\epsilon} \|u\|_{H^{\frac{3}{2}-\epsilon}(\Omega)}$$

- The discrete reduced problem is *spectrally equivalent* to the original one.
- Let $e_{(i)}$ and $e_{(ii)}$ be the modeling error related to the assumptions $(i), (ii)$, respectively. Then it holds:

$$\begin{aligned}
&\|e_{(i)}\|_{H^1(\Omega_p)} + \|e_{(ii)}\|_{H^1(\Omega)} \\
&\leq \left(1 + C_{PF}^2\right) \sum_{i=1}^{N} \left(C_{E,2}(\Omega_i) C_T(\Omega_p, \Gamma_i) C_{E,1}(\Omega_p, \Gamma_i)\right) \sum_{i=1}^{N} \|U_i\|_{H^{\frac{1}{2}}(\Gamma_i)} \\
&+ \frac{3}{4} \left(1 + C_{PF}^2\right)^2 \left(1 + C_T(\Omega_p, \Gamma_i) \sum_{i=1}^{N} \kappa_i\right) \sum_{i=1}^{N} \kappa_i |\Gamma_i| U_i^2 ,
\end{aligned}$$

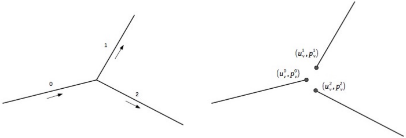
# Developments: Coupled mixed formulation

**From primal to mixed problem formulation:** (with D. Notaro, Ing. Mat)

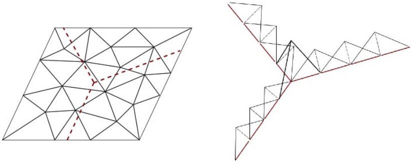
$$
\begin{cases}
-\frac{k}{\mu}\Delta p_t - f(\overline{p}_t,\overline{p}_v)\delta_\Lambda = 0 & in\ \Omega \\
-\frac{R^2}{8\mu}\frac{\partial^2 \overline{p}_v}{\partial s^2} + \frac{1}{\pi R^2} f(\overline{p}_t,\overline{p}_v) = 0 & in\ \Lambda
\end{cases}
\qquad
\begin{cases}
\frac{\mu}{k}\,\mathbf{u}_t + \nabla p_t = 0 & in\ \Omega \\
\nabla\cdot\mathbf{u}_t - f(\overline{p}_t,\overline{p}_v)\delta_\Lambda = 0 & in\ \Omega \\
\frac{8\mu}{R^2}\,\overline{u}_v + \frac{\partial \overline{p}_v}{\partial s} = 0 & in\ \Lambda \\
\frac{\partial \overline{u}_v}{\partial s} + \frac{1}{\pi R^2} f(\overline{p}_t,\overline{p}_v) = 0 & in\ \Lambda
\end{cases}
$$

**Challenges:**

- Enforcement of **mass conservation** at network nodes;




- Choice of **compatible** FEM spaces;



# Developments: Coupled mixed formulation

**Primal mixed:** Find $\mathbf{u}_t \in \mathbf{V}_t \subset \mathbf{L}^2(\Omega)$, $p_t \in Q_t \subset H^1(\Omega)$, $u_v \in V_v$, $p_v \in Q_v$

$$\begin{cases} (\frac{1}{\kappa_t}\mathbf{u}_t, \mathbf{v}_t)_\Omega + (\nabla p_t, \mathbf{v}_t)_\Omega = 0 \\ -(\mathbf{u}_t, \nabla q_t)_\Omega + (Q(\overline{p}_t - p_v), \overline{q}_t)_\Lambda + (\mathbf{u}_t \cdot \mathbf{n}_t, q_t)_{\partial\Omega} = 0 \\ (\frac{\pi^2 R'^4}{\kappa_v} u_v, v_v)_\Lambda + (\pi R'^2 \partial_s p_v, v_v)_\Lambda = 0 \\ -(\pi R'^2 u_v, \partial_s q_v)_\Lambda + (Q(p_v - \overline{p}_t), q_v)_\Lambda + [u_v q_v]_{\Lambda^{in}}^{\Lambda^{out}} = 0 \end{cases}$$

**Theorem:** there exists a unique solution of the primal mixed problem.

**Error analysis:**

$$\mathbf{u} := [\mathbf{u}_t, u_v] \quad p := [p_t, p_v]$$

$$\|\mathbf{v}, q\|^2 := \|\mathbf{v}_t\|^2_{L^2(\Omega)} + \|v_v\|^2_{L^2(\Lambda)} + \|q_t\|^2_{H^1(\Omega)} + \|q_v\|^2_{H^1(\Lambda)}$$

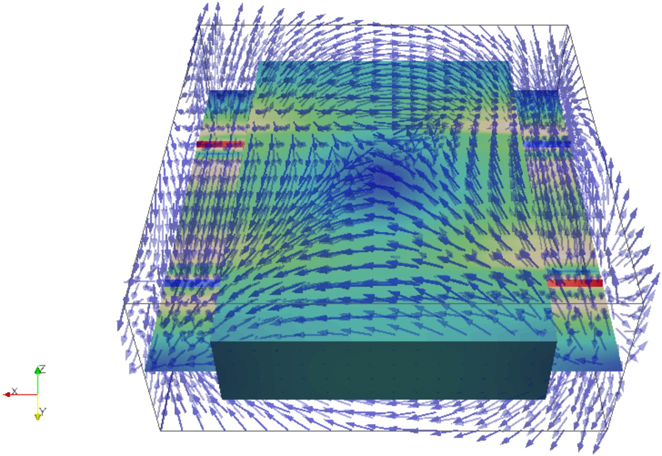
$$\|\mathbf{u} - \mathbf{u}_h, p - p_h\| \leq Ch^l \left[ |q_t|^2_{\mathbf{H}^{l+1}(\Omega)} + |q_v|^2_{H^{l+1}(\Lambda)} + |\mathbf{v}_t|^2_{\mathbf{H}^l(\Omega)} + |v_v|^2_{H^l(\Lambda)} \right]^{1/2}$$

D. Notaro, P. Zunino, Mixed Finite Element Methods for Coupled 3D/1D Fluid Problems, in preparation, 2016

# Developments: Coupled mixed formulation

**Mixed velocity-pressure approximation:**

- **Network:** $\mathbb{P}^2 - \mathbb{P}^1$ approximation of velocity and pressure;
- **Porous medium:** $\mathbb{RT}^0 - \mathbb{P}^0$ approximation of velocity and pressure;



# Applications: microcirculation and cancer

**Cancer alters blood perfusion**

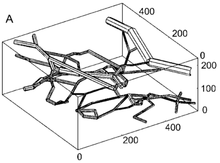
**Motivations:**

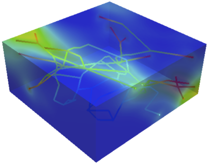
- understand the role of altered tumor vessel phenotype on tissue perfusion;
- understand alterations of mass transport;

**Objectives:**

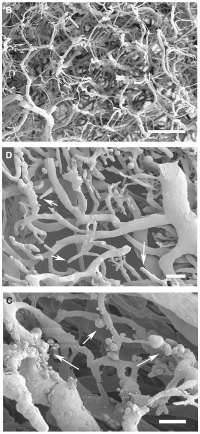
- build up a computational model able to capture the relevant physical phenomena on a **realistic microvascular geometry**;
- a **brute force approach** is computationally unfeasible;

courtesy of TW.Secomb



$P_{O_2}$ profiles 0-40 mmHg



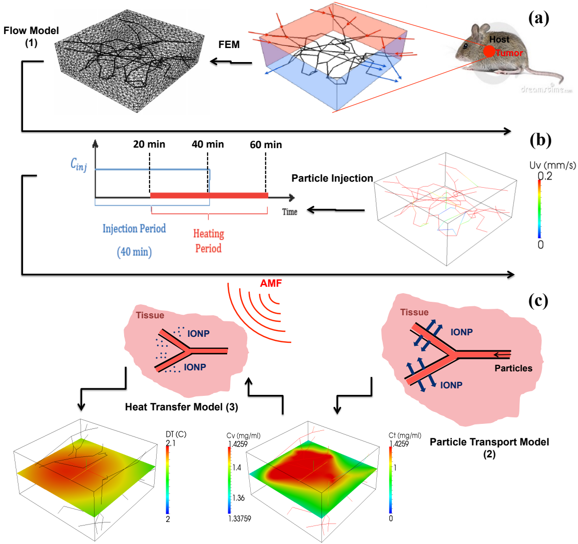

Vascular network of teratocarcinoma.

# Simulations: hypherthermic treatment

**Prototype study:** deliver iron oxyde nanocrystals thermally excited by electromagnetic fields, with **P. Decuzzi** and **M. Nabil**.

**A comprehensive simulator:**

- **Angiogenesis**;
- **Capillary and interstitial flow**;
- **Solute and particle transport**;
- **Heat transfer**;



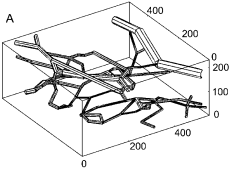

M. Nabil, P. Decuzzi and P. Zunino R. Soc. open sci. 2015 2 150447; DOI: 10.1098/rsos.150447 and R. Soc. open sci. 2016 3 160287; DOI: 10.1098/rsos.160287

# Conclusions: general applications

**Fluid mechanics: microvascular flows**

(3D) plasma pressure in tissue interstitium;

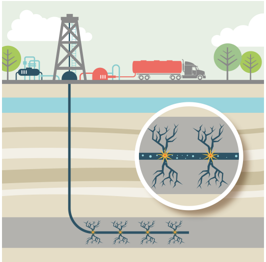
(1D) blood flow in microvessels;




**Fluid/solid mechanics: fracking**

(3D) geomechanics;

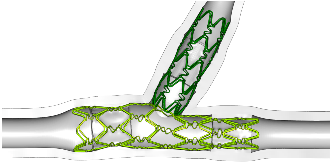
(1D/2D) flow in wells and fractures;



**Solid mechanics: biomedical devices**

(3D) mechanical stresses of tissue

(1D) mechanical stresses in the device



# Acknowledgements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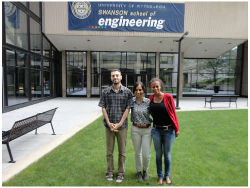
  **TUM & U.o.Stuttgart**, Germany
- L. Cattaneo Ph.D., Politecnico di Milano.
  **Ing. Mat.** PoliMi;
- M. Nabil, August 2013 - present, graduate student
  **Mechanical Engineering**, PennState;
- D. Notaro, A. Tiozzo, S. Brambilla, master students.
  **Ing. Mat.** PoliMi;


# Some recent works

**Tumor perfusion, drug delivery & hyperthermia:**


- Nabil M, Decuzzi P, Zunino P.; Modelling mass and heat transfer in nano-based cancer hyperthermia. R.Soc.Open Sci. (2015) 2: 150447.
- Cattaneo, L., Zunino, P. Numerical investigation of convergence rates for the FEM approximation of 3D-1D coupled problems (2015) Lecture Notes in Computational Science and Engineering, 103, pp. 727-734.
- Cattaneo, L., Zunino, P. A computational model of drug delivery through microcirculation to compare different tumor treatments (2014) International Journal for Numerical Methods in Biomedical Engineering, 30 (11), pp. 1347-1371.
- Cattaneo, L., Zunino, P. Computational models for fluid exchange between microcirculation and tissue interstitium (2014) Networks and Heterogeneous Media, 9 (1), pp. 135-159.


**Biomedical devices (stents):**


- P. Zunino, J. Tambača; E. Cutrì; S. Čanić; L. Formaggia; F. Migliavacca, Integrated stent models based on dimension reduction. Review and future perspectives. Annals of Biomedical Engineering, 44 (2), pp 604-617, 2015.
- C. D'Angelo, P. Zunino, A. Porpora, S. Morlacchi, F. Migliavacca, Model reduction strategies enable computational analysis of controlled drug release from cardiovascular stents, SIAM J. Appl. Math., Special Issue on Mathematical Modeling of Controlled Drug Delivery, Vol. 71 (2011) No. 6, pp. 2312-2333.