Mamba

MODELLING AND **A**NALYSIS FOR **M**EDICAL AND **B**IOLOGICAL **A**PPLICATIONS

Evaluation 2014 - 2017

October 12th, 2017

UPMC SORBONNE UNIVERSITÉS

Inria informatiques mathématiques

cnrs dépasser les frontières

Mamba

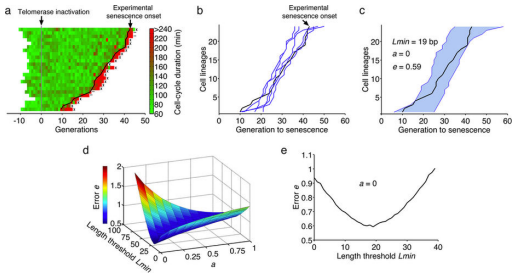
MODELLING AND ANALYSIS FOR MEDICAL AND BIOLOGICAL APPLICATIONS

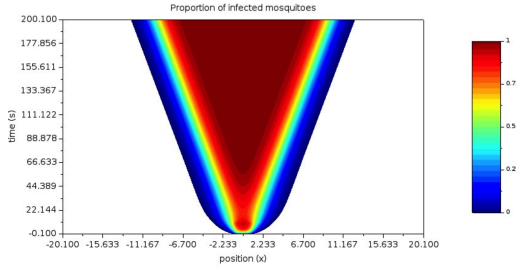
Combining Methods:

- integro & Partial Differential Equations (PDE)
- agent-based models (ABM), stoch. & stat. methods
- data assimilation, inverse problems

Towards medical and biological applications (including software development and transfer to biologists)

... and backwards, from medical problems to mathematical questions





Composition of MAMBA today - 26 members

Inria
P.A. Bliman since 2016,
J. Clairambault will retire 2018 & asks emeritus,
M. Doumic, D. Drasdo - new: D. Peurichard

LJLL (UPMC & CNRS)
L. Almeida, S. Mischler delegation 2017-2018, A. Lorz in leave,
B. Perthame - departure: N. Vauchelet in 2016 (prof. Paris 13)

Post-Doc: C. Carrere, P. Van Liedekerke, Y. Yin

PhD students: N. Boissier, F. Bubba, J. Delacour, G. Haddad,
S. Hanson, H. Martin, M. Mézache, C. Pouchol, A. Prunet,
A. Quillas Maran, M. Strugarek, C. Taing

Dortmund IfADo: T. Johann, A. Zaza, J. Zhao

Main events 2014-2017

- B. Perthame plenary ICM 2014 & Grand Prix Inria 2015
- End of M. Doumic's, beginning of B. Perthame's ERC grant
- D. Drasdo's associated team with Leipzig now followed by strong links with IfADo in Dortmund
- Strong link with WPI (Vienna) - M. Doumic & D. Peurichard
- Cancer: participation in 2 HTE projects funded in 2016
  J. Clairambault, M. Doumic, L. Almeida & D. Peurichard
- Wolbacchia project: strong interaction with Brazil
  P.-A. Bliman, B. Perthame, N. Vauchelet & L. Almeida

Miscellaneous scientific indicators

Future of young researchers

postdocs: academics or research engineers
predocs: academics, post-docs, companies (immediately hired)

Production: 13 Ph.D theses, 1 habilitation thesis, 95 articles:

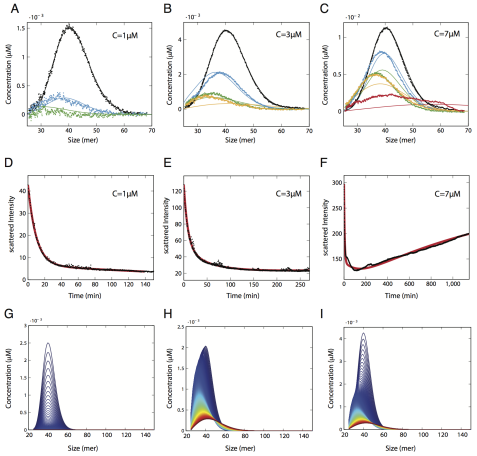
- Biology: 2 Nature Comm., 3 Hepatology, 1 Cancer Research, 1 Annals of surgery, 2 Archives of Toxicology.
- Interface: 6 PLoS, 5 J.Theor. Biol., 1 Bioinformatics, 3 J. Math. Biol., 1 Scientific Reports, 1 Inverse Problems.
- Maths: 4 M3AS, 2 JMPA, 5 SIAM, 1 J. Diff. Eq., 2 ARMA 5 KRM, 1 Nonlin Anal RWA, 1 Philos Tr R Soc Lond A

Many prestigious invitations, e.g.
M. Doumic plenary speaker ECMTB 2014
D. Drasdo plenary speaker Cyto 2015

Mamba's main collaborations

- Other INRIA project-teams:
Beagle, DISCO, Dracula, Lifeware, M3DISIM, Monc, Numed, RAP, Reo

[Illustration from PlOS One, 2017 - Mamba &M3DISIM]



- International: Brazil (IMPA, Rio de Janeiro; Fiocruz), China (Shanghai), Germany (German Cancer Center, Heidelberg - Leipzig), Israel (Weizmann Institute), Italy (Milan, Rome, Turin), Spain (Barcelona - BCAM, Bilbao, Granada, Madrid), Portugal (Lisbon), UK (Cambridge, Univ. Kent, Dundee, Edinburgh, Imperial College of London, Oxford, St Andrews), USA (NCSU, Raleigh; Maryland, Chicago), etc.

- Close collaboration: IfADo in Dortmund, WPI in Vienna

Strong partnership with biomedical teams

- INSERM (medical teams, cancer): St Antoine (Paris), Nantes
- Univ. of Kent in Canterbury (biophysics - protein aggregation)
- INRA (biophysics - protein aggregation)
- IBPC, Paris (yeast senescence)
- IBPS, Paris (early haematopoiesis and leukaemogenesis)
- Institut Jacques Monod (neurosciences)
- Curie Institute
- German Cancer Center (cancer), IfADo, Dortmund (toxicology)
- MFPL (Vienna - autophagy),

Research funds

Total funding amount raised in 2014-2017: $>$ 5M€

- ANR: BiMod, Kibord, IFLOW, iLite, InTelo
- INSERM: INVADE, INCA PCNSL
- ITMO Cancer: EcoAML & MoGIImaging
- IUF (Institut Universitaire de France)
- EU: NOTOX, 2 ERC: SKIPPER^{AD} & ADORA
- BMFB: LungSys II, Lebersimulator, LiSyM, MS-DILI
- STIC AmSud MOSTICAW & ECOS-NORD project
- M3CD EuroMed3+3 transmediterranean network
- DarEvCan National network (2012-2015)
- Sanofi contract

Research axes

Interactions between themes

Agent-Based Models & stochastic processes $\leftrightarrow$ continuous models

image analysis $\leftrightarrow$ data assimilation $\leftrightarrow$ statistics $\leftrightarrow$ modelling

evolution $\leftrightarrow$ cancer, polymerization $\leftrightarrow$ cell division

5 main axes:

$$\left.\begin{array}{l}\text{1. Population dynamics}\\ \text{2. Reaction and motion}\\ \text{3. From model to data}\end{array}\right\}\ \text{Methodological}$$

$$\left.\begin{array}{l}\text{4. Cancer}\\ \text{5. Growth, evolution}\\ \qquad\text{and regeneration}\end{array}\right\}\ \text{Application-driven}$$

Axis 1: analysis and control for population dynamics

Background: Long-standing "BANG" then MAMBA

many key contributions [B. Perthame, *Transport Equations in Biology*, 2007]

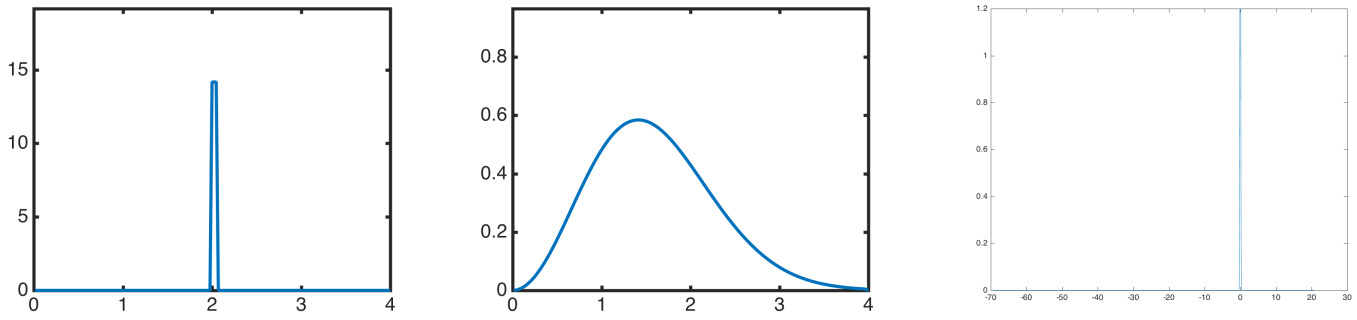
1 field, **many** applications $\Longrightarrow$ **new** math questions

Protein polymerization: Combining Lifshitz-Slyozov system with nonlinear growth-fragmentation equation

[J. Calvo, M. Doumic, B. Perthame, submitted]

Bacterial growth: "anomalous" asymptotics

strong link with stochastic processes (J. Bertoin *et al.*)



[M. Doumic, M. Escobedo, Kin. Rel. Mod., 2016]

Axis 1: analysis and control for population dynamics

Neuroscience: background

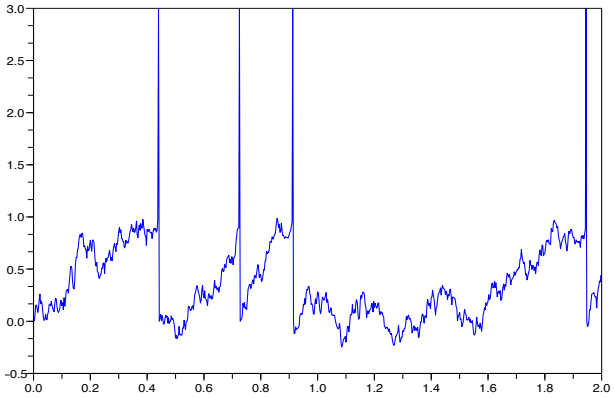
- neuroscientists, neurophysicists (N. Brunel, V. Hakim, D. Cai, K. Pakdaman),
- Inria teams (Paris-ICM, Nice, Bordeaux)

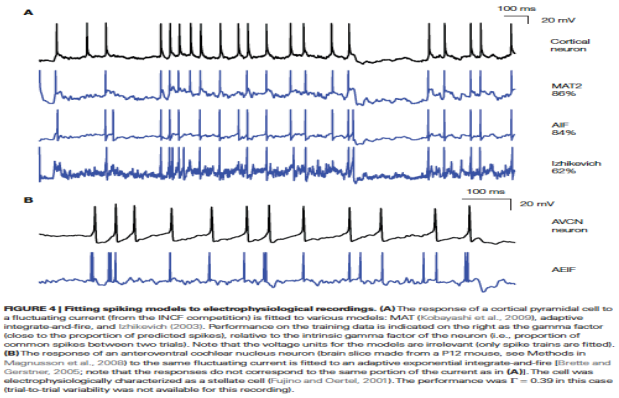
Equations:

- Class of mean-field limits of large assemblies of neurons
- Related to fragmentation equations

Questions: Synchronisation or not, analysis, learning...

Discoveries: Relation to Hawkes processes, Blow-up phenomena





Leaky Integrate and Fire models. Right: from R. Brette

[J. Carrillo, B. Perthame, D. Salort, D. Smets, Nonlinearity, 2015]

[M. Caceres, J. Chevallier, M. Doumic, P. Reynaud, M3AS 2015]

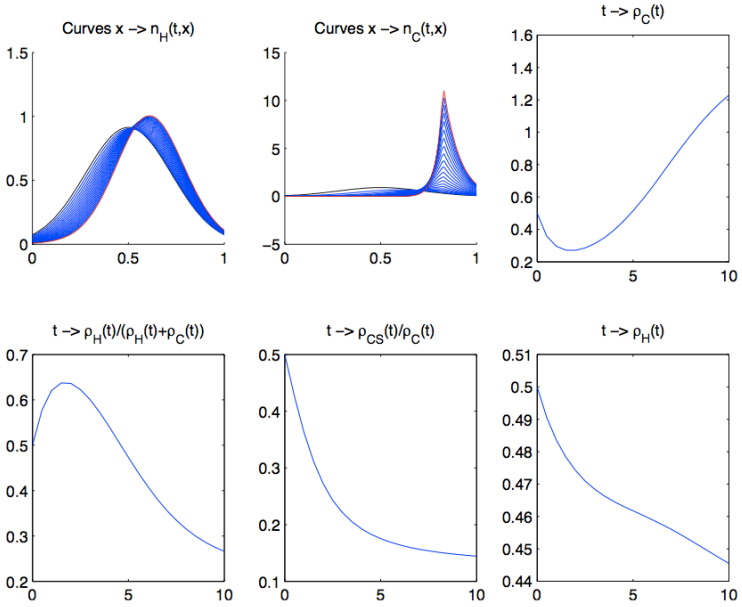
Axis 1: analysis and control for population dynamics

Resistance in cancer: background:

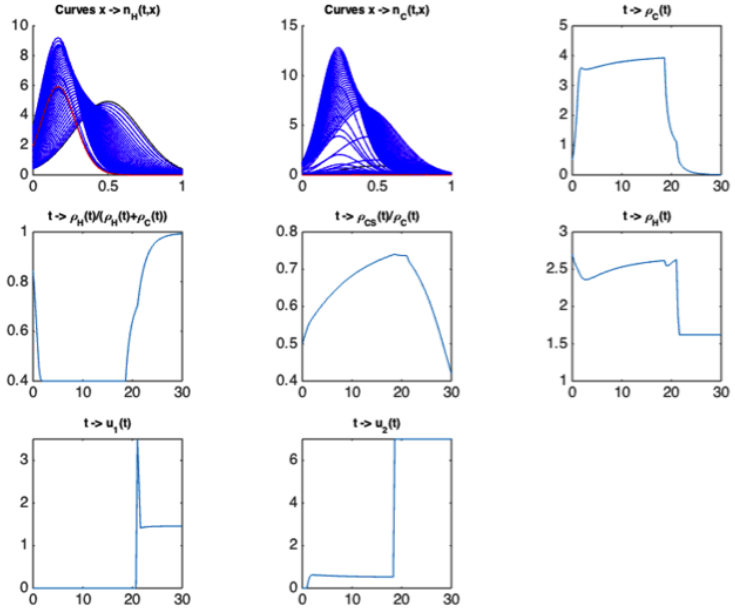
- adaptive dynamics, 2 competing populations
- phenotypically-structured equation

Question: asymptotics and control of combined anticancer drug

Constant doses of cytotoxic drugs select resistant cells.



an optimal control strategy (optimization using AMPL-IPOPT)



[C. Pouchol, J. Clairambault, A. Lorz, E. Trélat, accepted in JMPA]

Axis 1: analysis and control for population dynamics

Control of mosquito populations (Wolbachia): background:

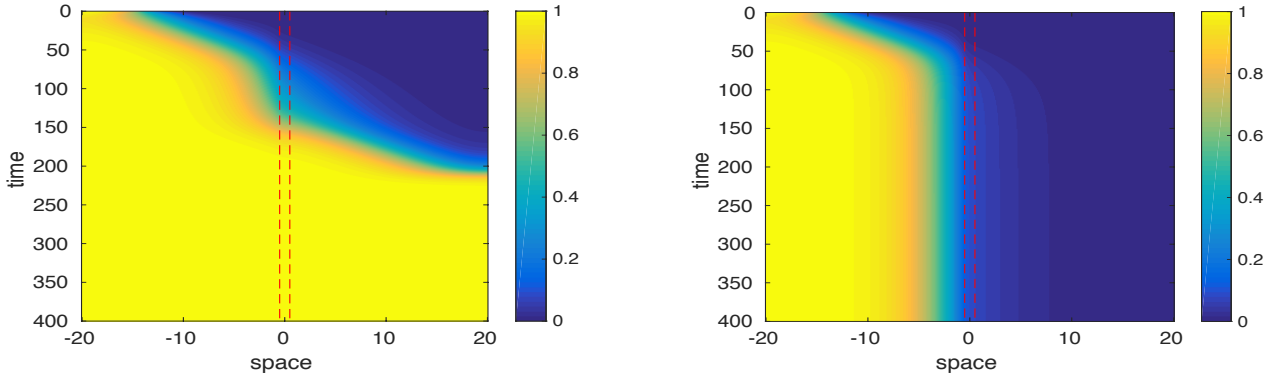
- Major public health problem (french polynesia)
- Fiocruz, Cirad, Institut Louis Malardé
- Launched by N. Vauchelet [N. Vauchelet, M. Strugarek, SIAP 2016]

Bistable propagation equation (Barton-Turelli)

$$\boxed{\partial_t p - \Delta p - 2\nabla p \cdot \frac{\nabla N}{N} = f(p)}$$

$p =$ proportion of infected mosquitoes

Questions: Rigorous derivation by asymptotic analysis, control of invasion, optimization of mosquitoe release



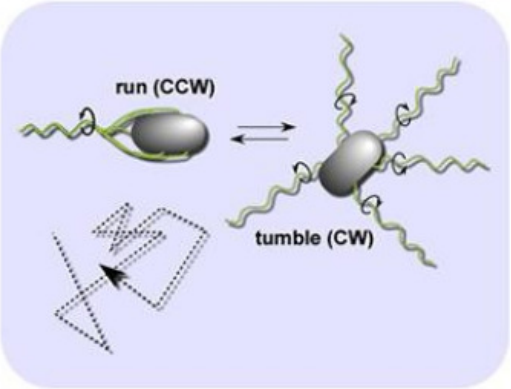
Succesfull and un-successful invasion

Axis 2: Reaction and motion equations

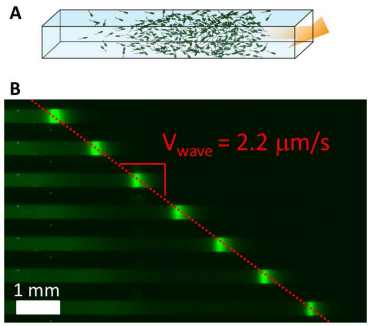
Bacterial chemotaxis

Micro: *run-and-tumble* process

Meso: kinetic system



- Asymptotic limits from mesoscopic to macroscopic systems
- Interaction of two species - travelling bands - **Institut Curie**
- singular solutions to models of strong aggregation
- numerical schemes to capture the dynamics at different scales.



[C. Emako, L. Almeida, N. Vauchelet *et al*, PLoS Comp Biol, 2016]

Axis 2: Reaction and motion equations

Free boundary problems for tumor growth

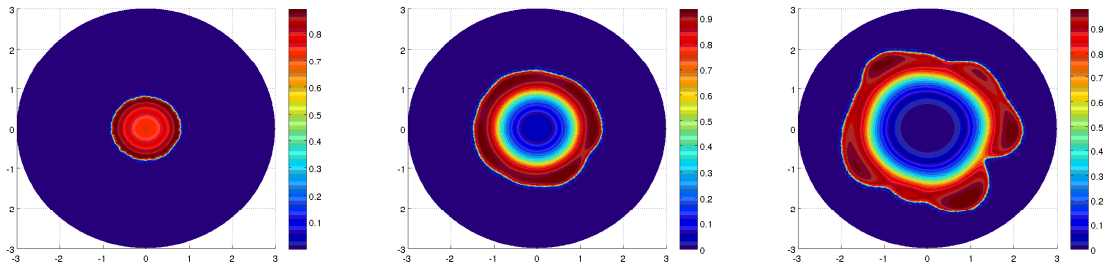
Two main classes of continuum models:

- dynamics of the density of tumoral cells subjected to a mechanical stress
- dynamics of its geometrical domain thanks to a Hele-Shaw type free boundary model

Result: link between the 2. [B. Perthame et al., ARMA 2014]

Second class obtained rigorously by incompressible limit of the first.

[B. Perthame, N. Vauchelet, Phil. Trans. Roy. Soc. Lond. A, 2015]

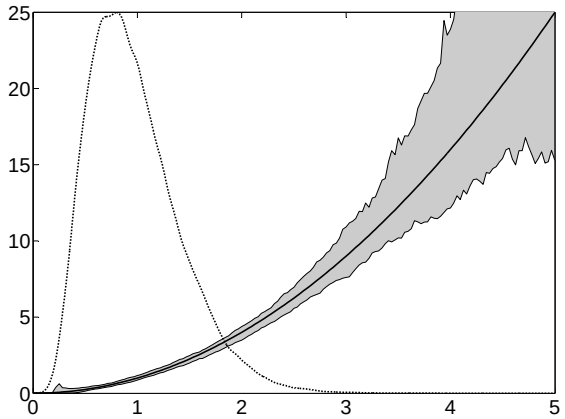


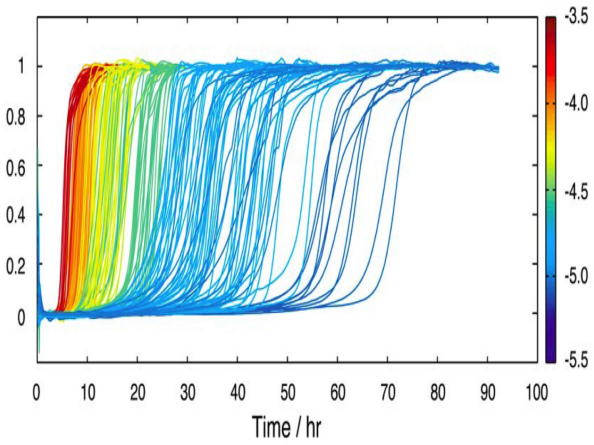
From [Perthame, Tang, Vauchelet, M3AS, 2014].

Axis 3: From model to data in nonlocal, multi-scale models

Combining statistical methods, data assimilation, probabilistic and PDE approaches

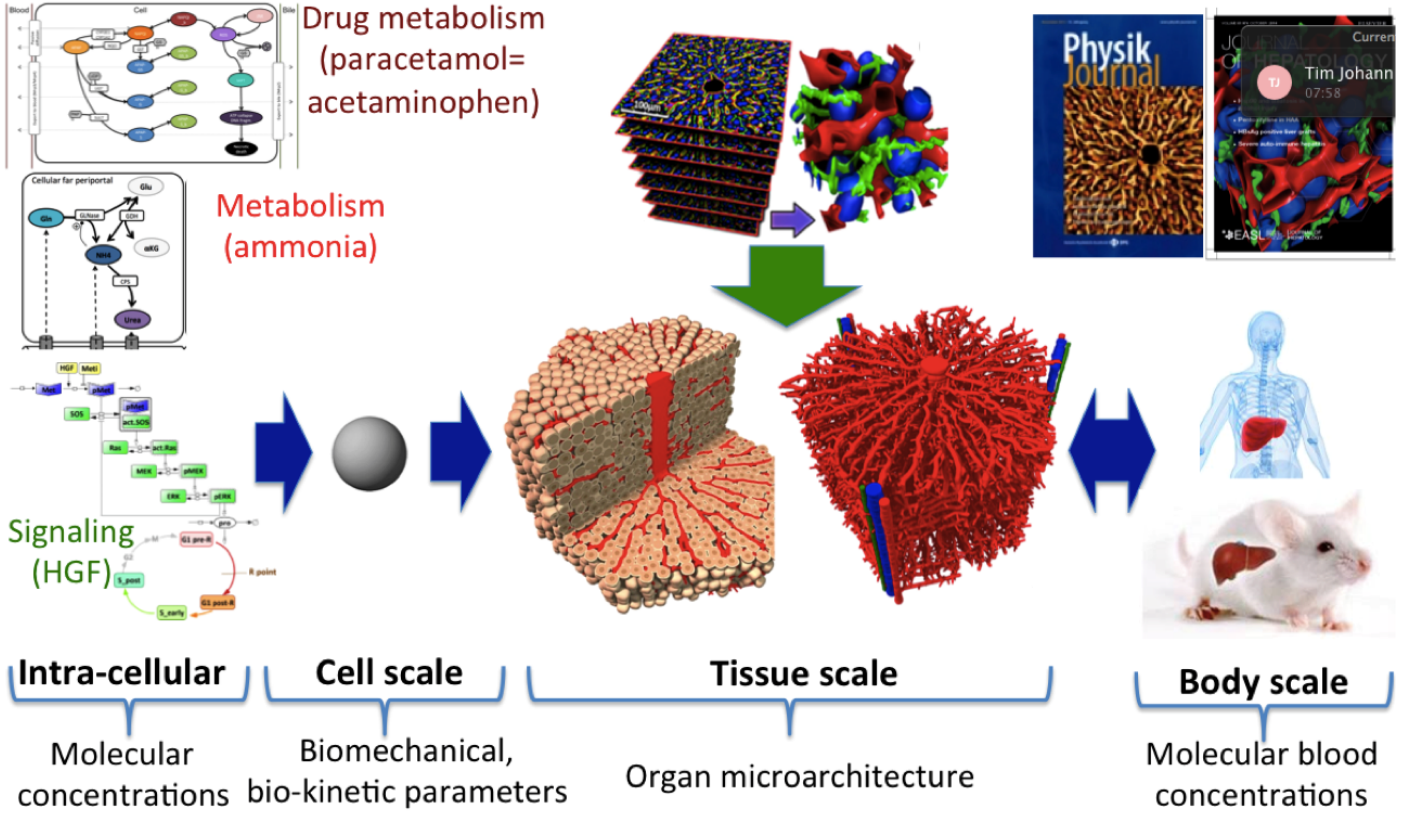
Estimating the birth/jumping/division rate
Link Piecewise Deterministic Markov Process (PDMP) with integro-PDE
[M. Doumic, M. Hoffmann et al., Bernoulli, 2015]





Data assimilation and stochastic modelling for protein aggregation
Use the variability as an information
[M. Doumic, S. Eugène, P. Robert, SIAP 2016]

Axis 3: From model to data in nonlocal, multi-scale models



[Drasdo et. al. J. Hepat. 2014]

[Drasdo et. al., Arch Tox 2014]

[D'Alessandro et.al. Progr. Biophys. & Mol. Biol. 2015]

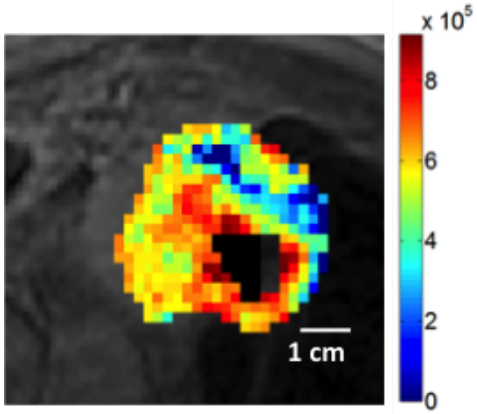
Intracellular: statistical methods for parameter and model identification in vitro, ex vivo and in vivo data.

Cell scale: sensitivity analyses within physiological parameter ranges.

Tissue scale: statist. representative microarchitecture from image reconstruction to define boundary condition for flow, pressure, transport.

Body scale: direct parameter identification from experiments.

Axis 4: Focus on cancer

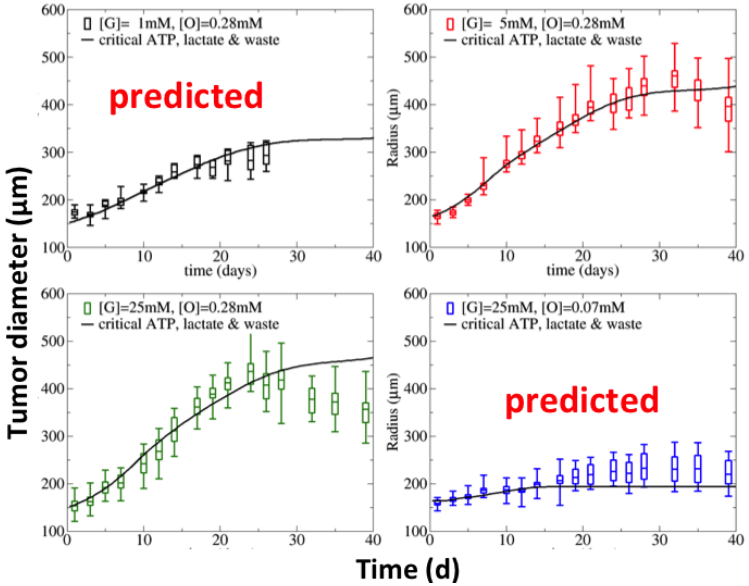


Estimation of cellularity & heterogeneity in non-small cell lung cancer from DW-MRI by calibration with histological data

[Yin... Vignon-Clémentel*, Drasdo*, IEEE TMI, 2017]

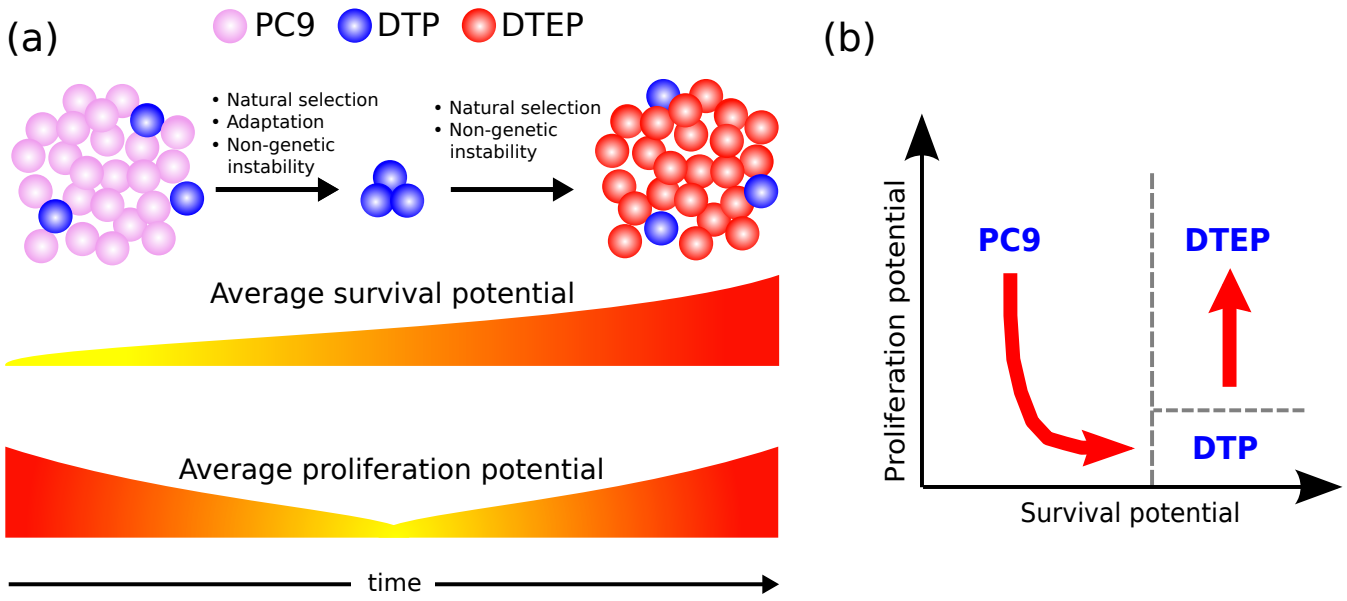
Predictive multiscale model of lung cancer multicellular spheroid growth by iterative image data integration and statistical evaluation of models.

[Jagiella... Vignon-Clémentel, Drasdo, PloS Comput Biol 2015]



Axis 4: Focus on cancer

- Spatio-temporal dynamics of signalling pathways: **p53**
- Early stages in AML: ongoing PhD theses, HTE programs
- Senescence and telomere modelling [Bourgeron et al., Sc. Rep., 2015]
- Drug-induced emergence of resistant cells in an aggressive lung cancer: parallel ABM & PDE models explain experimental data (Sharma et al., Cell 2010)



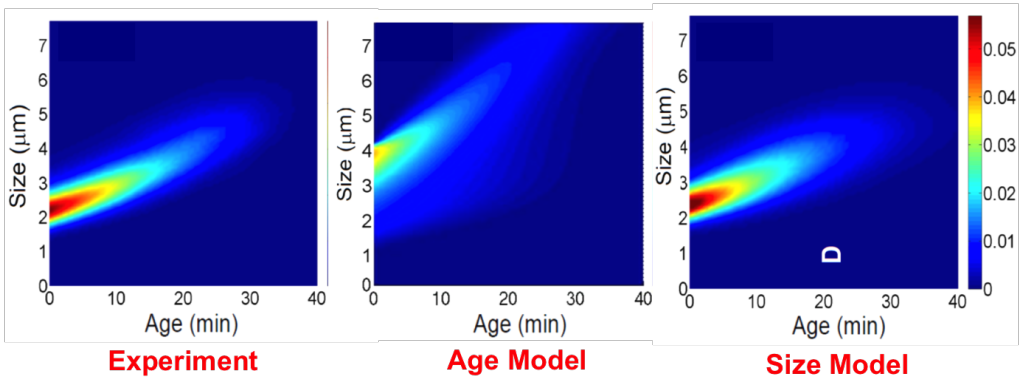
[Chisholm et al., Cancer Research 2015]

Axis 5: Growth, evolution and regeneration

Transfer to biology & medicine of the previous methods

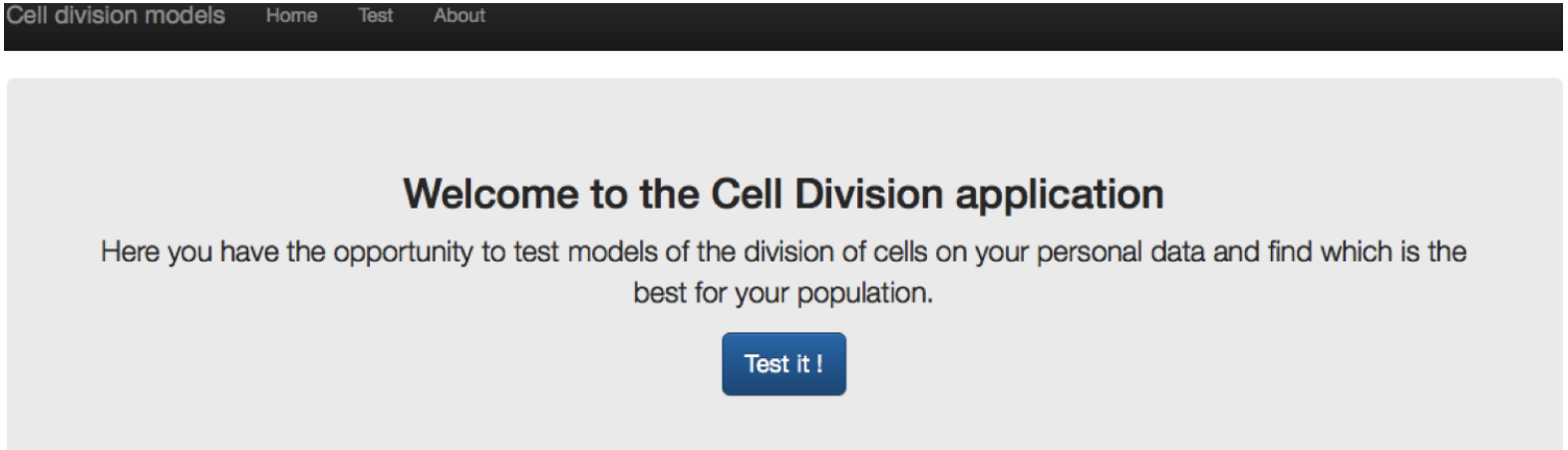
What triggers bacterial division?

[L. Robert,... M. Doumic*, BMC Biology, 2014]



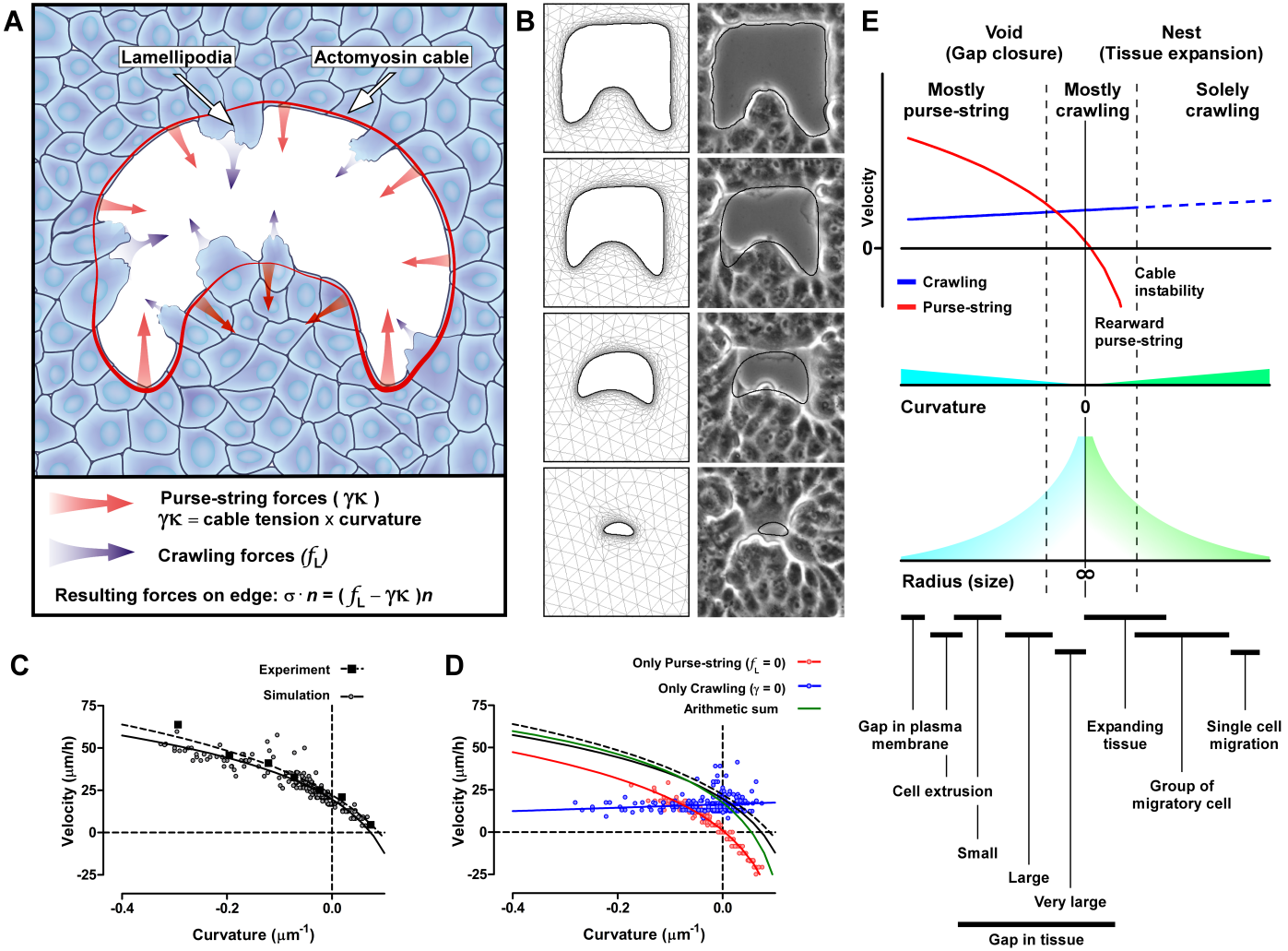
New model: not size but "increment" triggers division

New questions: analysis - model selection - software



Axis 5: Growth, evolution and regeneration

Mechanisms for wound healing and tissue repair



[A. Ravasio,..., L.Almeida and B. Ladoux, Nature Comm., 2015]

Axis 5: Growth, evolution and regeneration

Transfer to biology & medicine of the previous methods

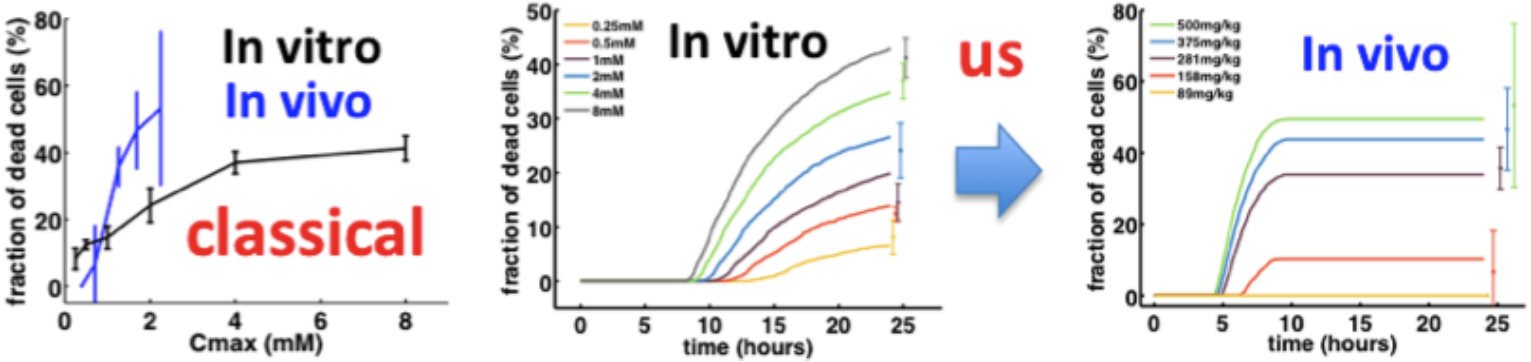
- Model shows failure of consensus model for ammonia detoxification in CCl4 or paracetamol-damaged liver & predicts ammonia sink mechanism.

  [Schliess, Hoehme... Drasdo*,Schliess*, Hepatology 2014]

- Model predicts reversible GDH mechanism as most likely of many options. Experimentally validated & potential therapy option.

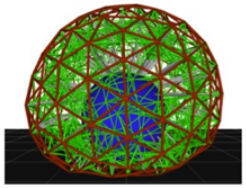
  [Ghallab, Celliere... Drasdo*, Gebhardt*, Hengstler*, J. Hepat. 2016]

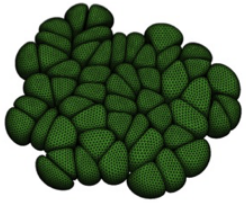
- Model-based prediction of in vivo paracetamol toxicity from in vitro data.

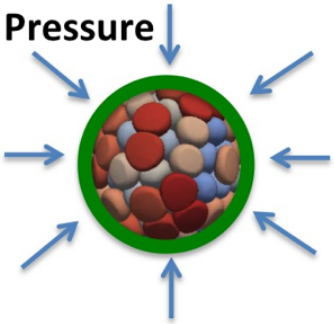


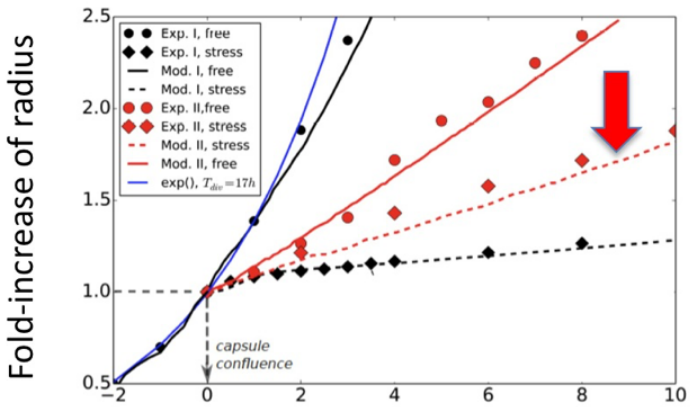
Axis 5: Growth, evolution and regeneration

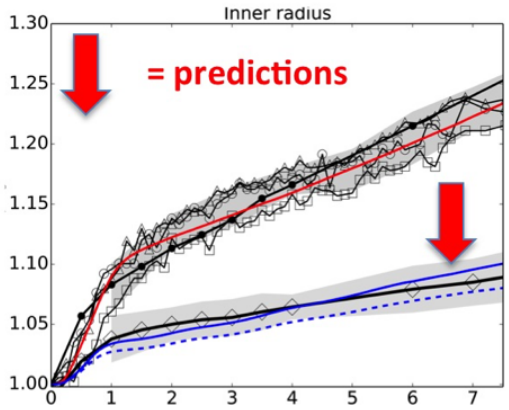
Transfer to biology & medicine of the previous methods

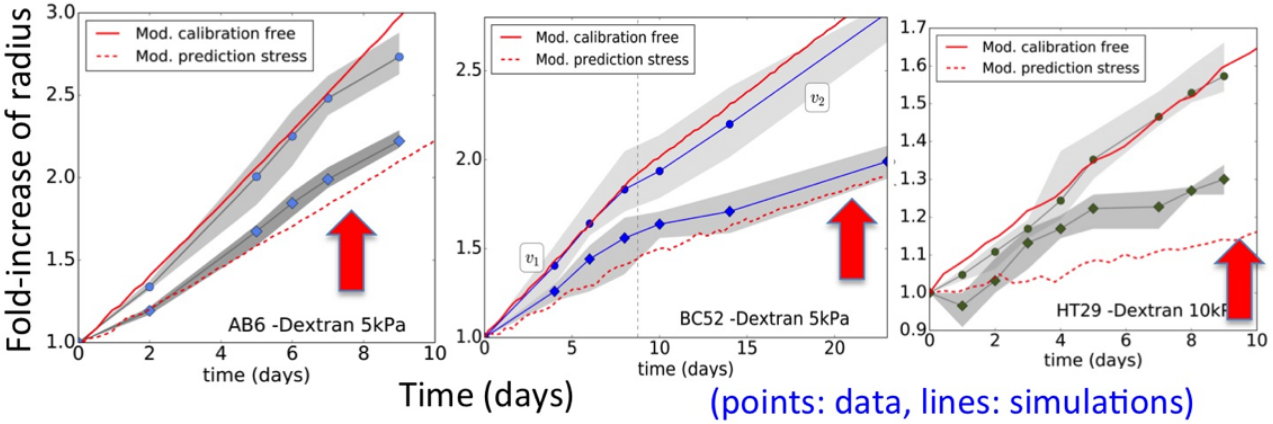




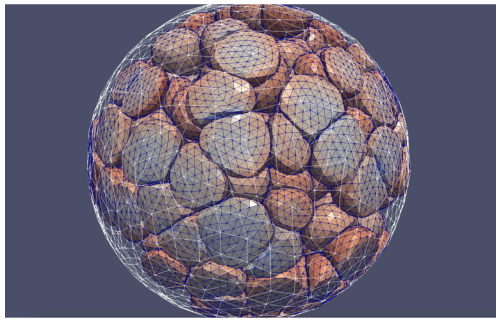








(points: data, lines: simulations)

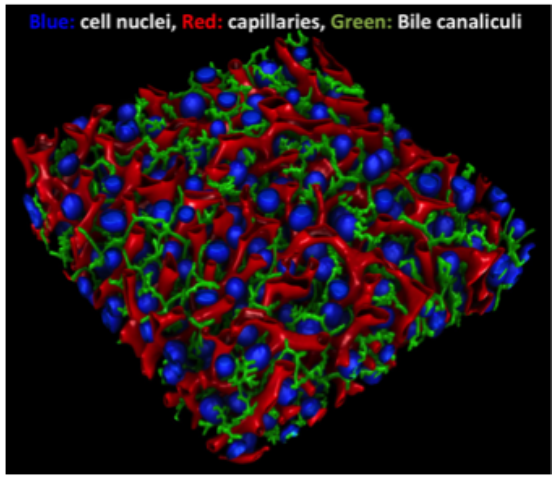


- Quantitative prediction of pressure-response in multicellular spheroids over different experimental conditions (capsule, Dextran) and cell lines with hybrid agent-based model [Liedekerke et al, in rev.]

Software: TiQuant & TiSim

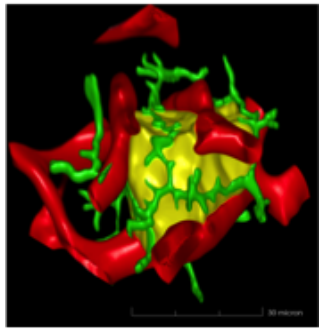
- **TiQuant**: Image processing, analysis and quantication (with Hoehme group/Univ. Leipzig). Downloadable. Next version uses machine learning approach.

  [Friebel et al., Bioinformatics 2015; Hammad et al. Arch. Toxicol. 2014]



- Multiscale modeling: all simulations performed in new tool TiSim (Tissue Simulator). Modular, includes agent (center-) based models for monolayers, multicellular spheroids, liver regeneration; delivery in preparation. In follow-up: deformable cell models, ECM etc.

  [Johann et.al., in preparation]



Objectives for the next four years

Unchanged roadmap:
Towards medical and biological applications (including software development and transfer to biologists)
and backwards, from medical problems to mathematical questions

Staff evolution:

- D. Peurichard
  $\Longrightarrow$ strong collaboration with WPI (C. Schmeiser)
- P. Robert, Inria Rap
  $\Longrightarrow$ still more merging PDE/stochastic processes
- J. Clairambault's retirement: emeritus & implication of L. Almeida, M. Doumic, D. Peurichard in HTE cancer projects

Objectives for the next four years

Some specific objectives / new orientations:

- Living tissues, regeneration, carrying results to clinics and toxicology
  L. Almeida, D. Drasdo, D. Peurichard, B. Perthame
- Division rate estimation $\Longrightarrow$ new applications
  M. Doumic, P. Robert
- Dengue fever control $\Longrightarrow$ Difficulty: N. Vauchelet's departure
  L. Almeida, P.-A. Bliman
- Evolution models for cancer cell populations: HTE projects / data
  L. Almeida, J. Clairambault, D. Peurichard
- Mathematical analysis of PDE models of neural networks
  M. Doumic, B. Perthame


solution
tumor
cell
equation
analysis
cancer
fragmentation
kinetic
liver
drug
evolution
boundary
problem
estimation
networks
data
tissue
division
control
transport
methods
amyloid
protein
p53
conservation
Traveling
Dynamics
amba