Mathematical modelling of (hydrocephalus and) the infusion test

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Outline

A little history

Monro (1783)	Solid skull, incompressible tissue $\rightarrow$ Total blood volume = constant
Kellie (1824)	Blood volume + cerebral CSF volume = constant
(1970's, 1980's)	Circuit analogy, animal models
Davson et al. (1973)	Constant CSF outflow resistance
Marmarou et al. (1975)	Exponential pressure-volume curve, pressure-dependent compliance $\rightarrow$ Basis for current compliance models

Derivation of model equation

- CSF volume balance $\frac{\mathrm{d}V}{\mathrm{d}t} = Q_{\text{inflow}} - Q_{\text{outflow}}$
- Pressure-dependent outflow $Q_{\text{outflow}}(p) = \frac{p - p_{\text{sss}}}{R}$
- Known (often constant) inflow
  $Q_{\text{inflow}} = Q_{\text{production}} + Q_{\text{infusion}}(t)$
- Baseline pressure before the infusion
  $Q_{\text{production}} = Q_{\text{outflow}}(p_{\text{b}}) = \frac{p_{\text{b}} - p_{\text{sss}}}{R}$
- Subtract CSF production rate, $\frac{\mathrm{d}V}{\mathrm{d}t} = Q_{\text{infusion}}(t) - \frac{p - p_{\text{b}}}{R}$
- Chain rule with known compliance function
  $\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{\mathrm{d}V}{\mathrm{d}p}\frac{\mathrm{d}p}{\mathrm{d}t} = C(p)\frac{\mathrm{d}p}{\mathrm{d}t}$
- Combining everything
  $C(p)\frac{\mathrm{d}p}{\mathrm{d}t} = Q_{\text{infusion}}(t) - \frac{p - p_{\text{b}}}{R}$

Standard compliance function

- Marmarou et al. (1975): Exponential pressure-volume curve $p = p_\mathrm{b} \exp(E\,V)$ yields compliance $C(p) = \frac{1}{E\,p} = \frac{\mathrm{PVI}}{\ln(10)\,p}$
- Standard compliance function used nowadays $C(p) = \frac{1}{E\,(p - p_0)}$
- Value and importance of reference pressure p_0 unclear, e. g. zero or pressure in superior sagittal sinus
- For constant infusion test and this compliance, there is an analytic solution of ODE $\frac{1}{E\,(p-p_0)} \frac{\mathrm{d}p}{\mathrm{d}t} = Q_\mathrm{infusion} - \frac{p - p_\mathrm{b}}{R}$
- Parameters can be estimated by fitting the pressure curve to infusion test data
- Note that E and p_0 are closely linked in compliance

Generalised compliance function

- Standard compliance function used nowadays $C(p) = \frac{1}{E\,(p-p_0)}$
- Parameter estimations indicate pressure-dependence of E
- Wirth & Sobey (2008) generalise compliance function

$$C(p) = \frac{1}{\tilde{e}\,(p-p_0)^n} = \frac{1}{\tilde{e}(p-p_0)^{n-1}\,(p-p_0)} = \frac{1}{E(p)\,(p-p_0)}$$

  from collapsing veins
- Three parameters $\tilde{e}$, p_0, and n for compliance
- Standard model is special case $n = 1$
- In general no analytic solution. Need numerical integration.
  $\rightarrow$ Parameter estimations more computationally expensive

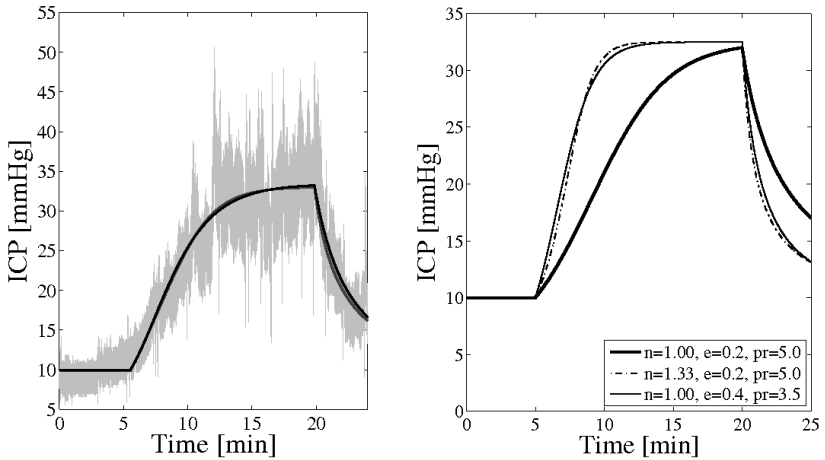
Standard vs. generalised compliance function I

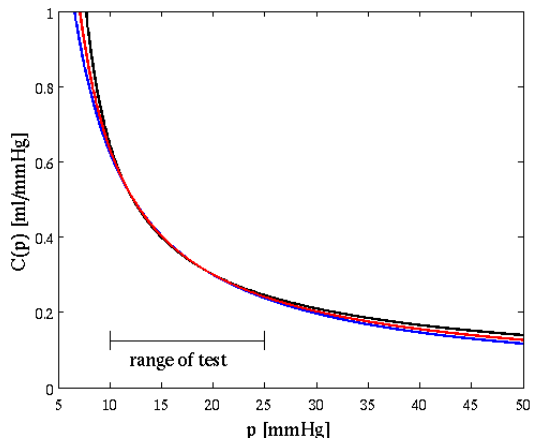
- Variations of all five parameters (and combinations)
- Parameter estimations (method)
  - Automatic: input only measured ICP, infusion rate & times
  - consider only time before and during infusion
  - variant of least squares minimisation
  - repeat with pseudo-random initial parameter sets
- Parameter estimations (application)
  - tested with artificial data sets ($n = 1$, $n = 0.7$, n variable)
  - 7 infusion tests that reach plateau pressure (only fixed power n: 1 standard, 0.7 generalised)

Eisenträger et al. (2012)

Standard vs. generalised compliance function II

- Both models "work"
- Different parameter sets yield similar output $\rightarrow$ local minima
- Generalised model ill-defined for certain parameter regions
- Workaround: Repeat with pseudo-random initial parameter sets
- Parameters $\tilde{e}$ (or E), p_0 and n
  - are dependent $\rightarrow$ neither is helpful alone
  - together encode compliance C as a function of pressure
  - but *only* over the pressure range of the test





Eisenträger et al. (2012)

A little more history

Biot (1941) Consolidation Theory
= Theory of Poroelasticity

Hakim et al. (1976) First biomechanical model of brain and CSF (as "sponge")

Nagashima et al. (1987) Use Biot's theory to model brain as a poroelastic material

(1990's, 2000's) Various poroelastic models of hydrocephalus development,

- often simplified geometry
- mostly pressure boundary conditions
- analytic/numerical solution
- some include pressure oscillations

Wirth & Sobey (2009) Poroelastic model of infusion test

- spherical symmetry
- flow boundary conditions incl. aqueduct
- arterial blood pressure oscillations

Poroelastic governing equations

Fluid pressure p

Solid displacement U

Strain of solid (linearised)

$$\mathcal{E} = \frac{1}{2}\left(\nabla U + \nabla U^T\right)$$

Volume dilation $\epsilon = \mathrm{tr}(\mathcal{E})$

Combined stress (Terzaghi)

$$\begin{aligned}\sigma &= \sigma_{\text{solid}} + \alpha\sigma_{\text{fluid}} \\ &= (\lambda\epsilon I + 2\mu\mathcal{E}) - \alpha p I\end{aligned}$$

Conservation of momentum

$$\nabla \cdot \sigma = 0$$

Darcy flow through porous solid

$$q = -\frac{k(\epsilon)}{\eta}\nabla p$$

Fluid content increase

$$\zeta := \frac{V_f - V_{f,0}}{V_0} = \alpha\epsilon + \gamma(p)p$$

Fluid volume balance

$$\frac{\partial \zeta}{\partial t} = -\nabla \cdot q$$

$$\Rightarrow \alpha\frac{\partial \epsilon}{\partial t} + \frac{\partial}{\partial t}\left(\gamma(p)p\right) = \nabla \cdot \left(\frac{k(\epsilon)}{\eta}\nabla p\right)$$

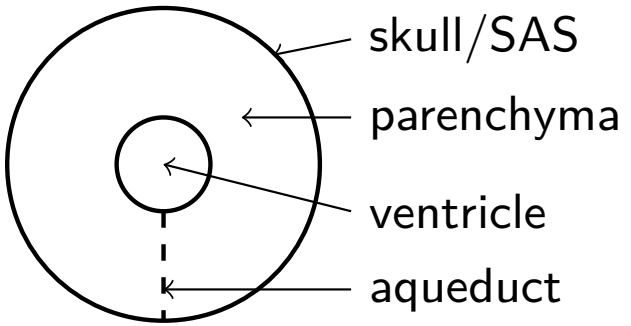
Spherical symmetry

Need only 1 spatial dimension

$$\epsilon = \frac{\partial u}{\partial r} + 2\frac{u}{r}$$

$$(\lambda + 2\mu)\frac{\partial \epsilon}{\partial r} - \alpha\frac{\partial p}{\partial r} = 0$$

$$\alpha\frac{\partial \epsilon}{\partial t} + \frac{\partial}{\partial t}\Big(\gamma(p)p\Big) = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{k(\epsilon)}{\eta}\frac{\partial p}{\partial r}\right)$$



Integrate:

$$u(r,t) = \frac{1}{r^2}\left(\int_{r_\star}^{r} s^2\epsilon(s,t)\mathrm{d}s + r_\star^2 u_\star(t)\right)$$

$$p(r,t) = \frac{(\lambda + 2\mu)}{\alpha}\epsilon(r,t) + p_c(t)$$

$$\Rightarrow A(p)\frac{\partial \epsilon}{\partial t} + B(p)\frac{\partial p_c}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 k(\epsilon)\frac{\partial \epsilon}{\partial r}\right)$$

Boundary conditions

No displacement of solid at the rigid skull

$$u(r_{\text{out}}) = 0$$

Stress continuity across ventricle wall

$$(\text{radial combined stress at } r_{\text{in}}) = -p(r_{\text{in}}, t)$$

Fluid volume conservation in the ventricle and at the skull

$$\begin{aligned}(\text{CSF production}) &= (\text{increase in ventricle volume}) \\ &\quad + (\text{flow through aqueduct}) \\ &\quad + (\text{flow into porous tissue}) \\ (\text{CSF absorbtion}) &= (\text{flow through aqueduct}) \\ &\quad + (\text{flow out of porous tissue}) \\ &\quad + (\text{infusion})\end{aligned}$$

Extension to two fluid model

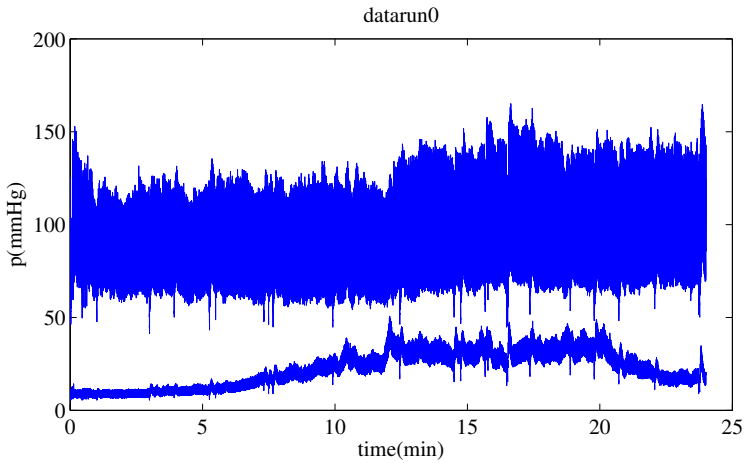
Include measured arterial blood pressure $p_{\text{ab}}(t)$ into

- stress

$$\begin{aligned}\sigma &= \sigma_{\text{solid}} + \alpha\sigma_{\text{CSF}} + \alpha_{\text{ab}}\sigma_{\text{ab}} \\ &= (\lambda\epsilon I + 2\mu\mathcal{E}) - \alpha p I - \alpha_{\text{ab}} p_{\text{ab}} I\end{aligned}$$

- increase in CSF content

$$\zeta = \alpha\epsilon + \gamma(p)p - \gamma_{\text{ab}} p_{\text{ab}}$$



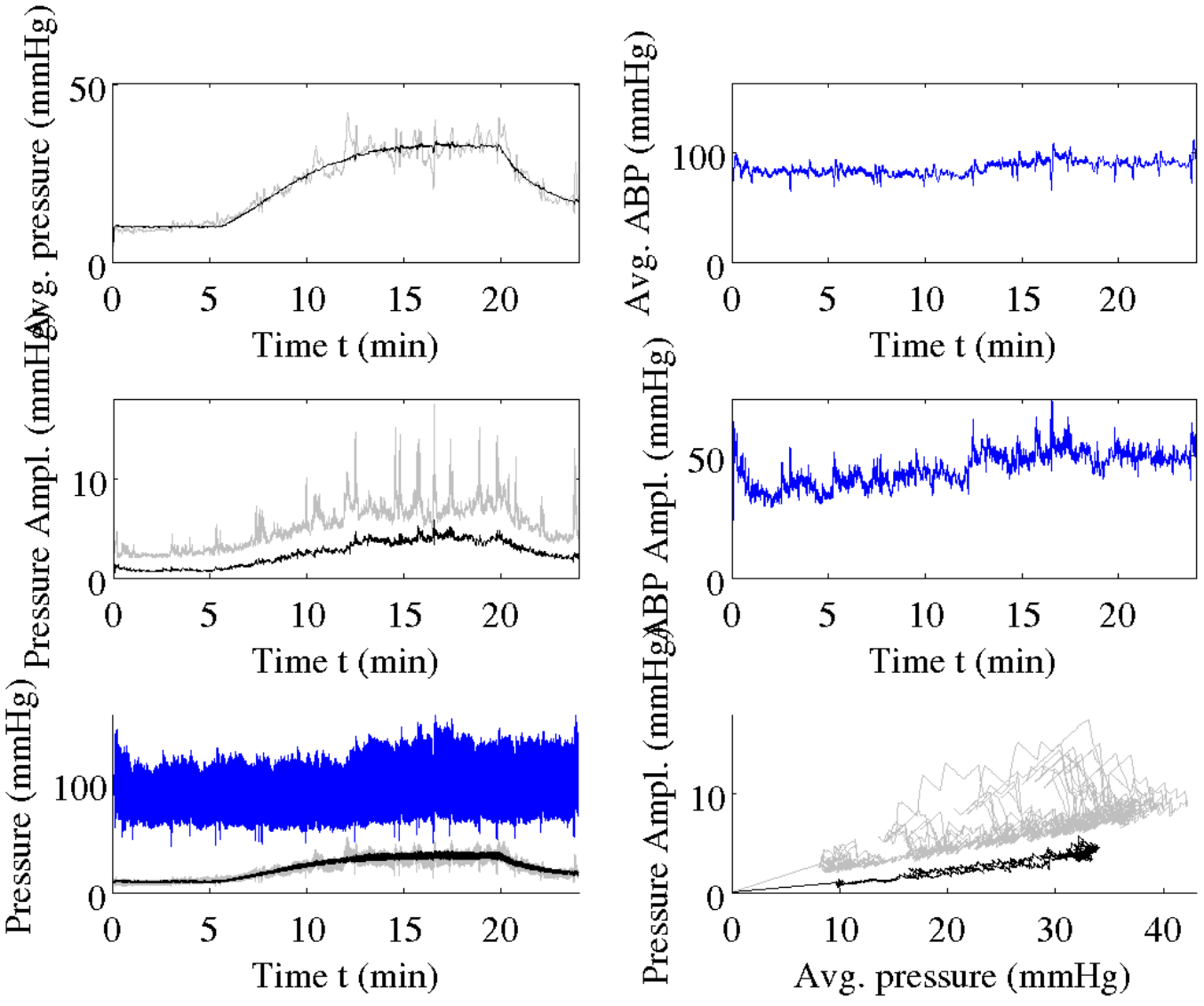
Arterial blood pressure (above) and CSF pressure (below)

yielding the equations

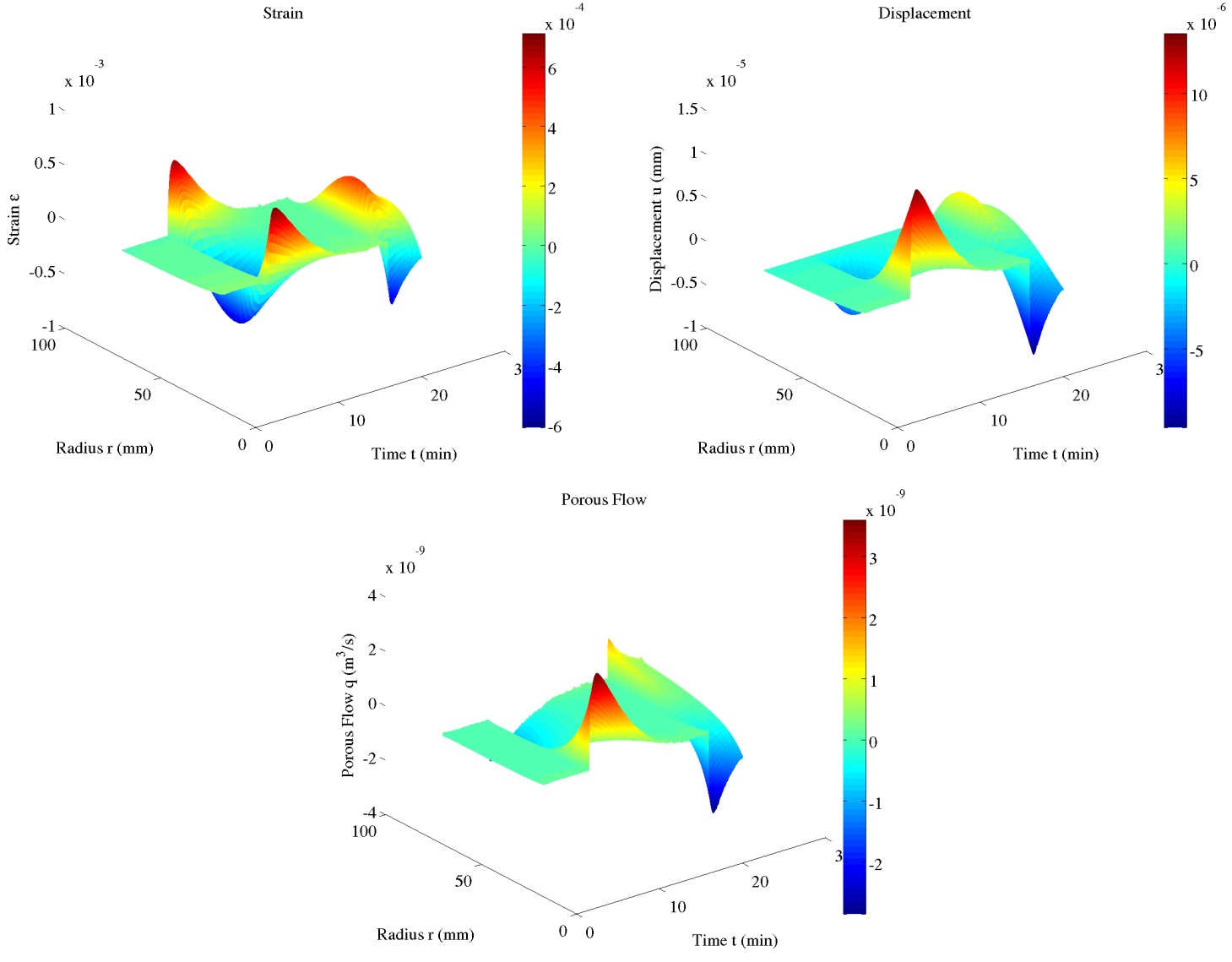
$$(\lambda + 2\mu)\frac{\partial \epsilon}{\partial r} - \alpha\frac{\partial p}{\partial r} = \alpha_{\text{ab}}\frac{\partial p_{\text{ab}}}{\partial r} = 0,$$

$$\alpha\frac{\partial \epsilon}{\partial t} + \frac{\partial}{\partial t}\Big(\gamma(p)p\Big) = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{k(\epsilon)}{\eta}\frac{\partial p}{\partial r}\right) + \gamma_{\text{ab}}\frac{\partial p_{\text{ab}}}{\partial t}$$

Results: pressure



Results: strain, displacements, porous flow



Space average model

- Fluid balance equation ($\alpha = 1$)

$$\frac{\partial \epsilon}{\partial t} + \frac{\partial}{\partial t}\Big(\gamma(p)p\Big) = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{k(\epsilon)}{\eta}\frac{\partial p}{\partial r}\right) + \gamma_{\text{ab}}\frac{\partial p_{\text{ab}}}{\partial t}$$

- Integrate over parenchyma volume $V_{\text{par}} = \int_{r_{\text{in}}}^{r_{\text{out}}} 4\pi r^2 \mathrm{d}r$, combine with boundary conditions, average pressure
- Collapses to single compartment model with arterial blood pressure oscillation

$$C(\bar{p})\frac{\mathrm{d}\bar{p}}{\mathrm{d}t} = Q_{\text{production}} + Q_{\text{infusion}}(t) - Q_{\text{outflow}}(\bar{p}) + C_{\text{ab}}\frac{\mathrm{d}p_{\text{ab}}}{\mathrm{d}t}$$

$$C(\bar{p}) = V_{\text{par}}\left(\frac{\mathrm{d}\gamma}{\mathrm{d}\bar{p}}\bar{p} + \gamma(\bar{p})\right) \qquad C_{\text{ab}} = V_{\text{par}}\gamma_{\text{ab}}$$

Sobey et al. (2012)

Other models

- Variants of compartment type models
  - Oscillatory source terms (blood flow or CSF flow into spine)
  - Focus on other infusion tests (e. g. constant pressure levels)
  - Multi-compartment models
- Variants of poroelastic models
  - different geometry, e. g. cylindrical, patient-specific
  - different boundary conditions
  - CSF sources/sinks in parenchyma
  - Multiple-Network Poroelastic Theory (MPET)
- Viscoelastic models (only solid phase)
  - various viscoelastic models (stress depends on strain-rate)
  - used for Magnetic Resonance Elastography (MRE)
- Fluid-Solid-Interaction (ventricles, subarachnoid space, spine)
- Hybrid models, . . .

Future directions

- Use compliance function rather than elasticity constant
- Better quantitative understanding of biological processes, e. g. autoregulation, slow waves, CSF production/absorbtion in parenchyma
- Measurements of mechanical/biological parameters and their variance (spatially, between patients, with age, . . .), e. g. via MRE
- Stochastic Differential Equations?
- Multi-scale modelling
- Linking models of brain and spine

- *Other ideas? Comments? Questions? . . .*

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