Joint risk-measurement model for the risk of decompression sickness accidents based on the biophysical model of decompression

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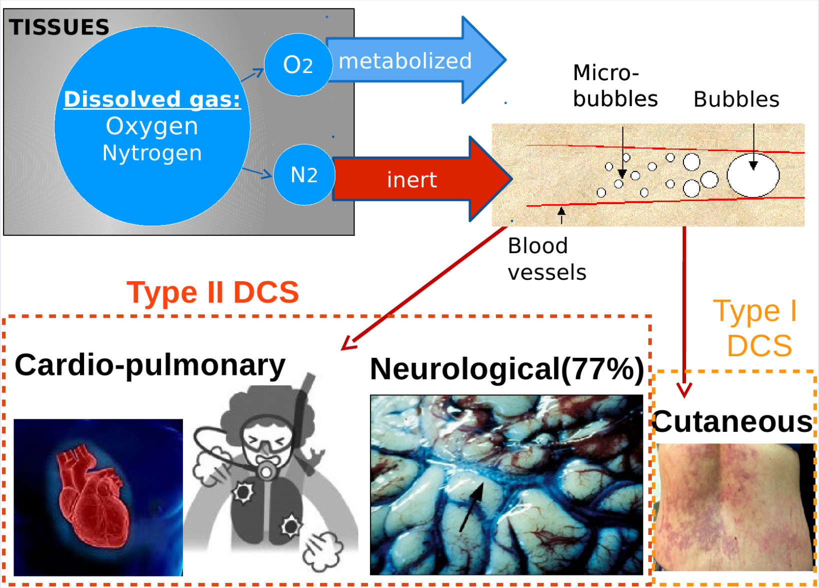
Plan:

1. Introduction
   - Decompression sickness accidents (DCS)
   - Biomarker of individual response to decompression.
   - Two competing classical approaches.
2. Main model
   - Individual risk model for DCS.
   - Joint risk measurement model.
   - Results: simulations and real data.
3. Conclusions
   - Discussion and perspectives

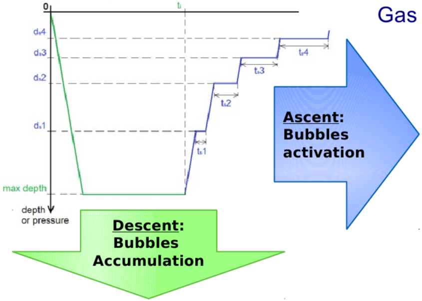
Introduction: Decompression Sickness Accidents

Diverse manifestations of decompression sickness accidents

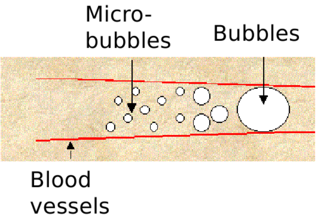


Biophysical mecansim of bubble formation

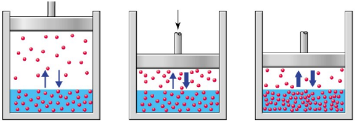
Dive profile



Effect of decompression :
Gas is transfered from tissues to blood and gas bubbles are growing



Effect of compression :
Gas is dissolved in tissues



(a) Initial equilibrium (b) Increased pressure (c) New equilibrium

The effect of bubbles

The formation of bubbles affects :

1. brain
2. spinal cord
3. cranial and peripheral nerves
4. neural vasculature

- Nitrogen bubbles can injure neural tissues by mechanical disruption, compression, vascular stenosis or obstruction, and activation of inflammatory pathways.
- Cerebral decompression sickness (30 to 40 percent of cases) usually involves arterial circulation.
- Spinal cord decompression sickness (50 to 60 percent of cases) involves obstruction of venous drainage and the formation of bubbles within the cord parenchyma

Symptomatology of neurological DCS

1. **Cerebral DCS**: Confusion, focal weakness, fatigue, visual loss, speech dysfunction, headache...
2. **Spinal cord DCS**: Paresthesias,sensory loss in trunk and/or extremities, leg weakness, loss of bowel/bladder function.
3. **Headache**: Severe generalized headache associated with alteration of consciousness

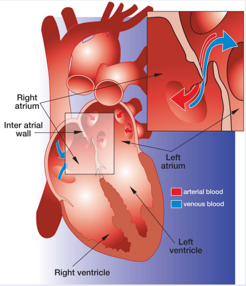
Event when no DCS occures, bubbles have a damaging effect on endothelium: reduced endothelial function after exposure.

Characteristics of DCS

- Strong iter-individual and intra-individual variability: same dive P can produce few or many bubbles, with a variation in the response to bubbles.
- Rare event: incidence about 1 per 10000.
- 50% of DCS cases occures when respecting decompression procedure.

Risk factors for DCS

- **Exposure: depth and duration of dive.**
- **Decompression: short ascent time**
- Repetivive dives.
- **Gas breathed: air, nitrox.**
- PFO (Patent Foramen Ovale)
- others ...



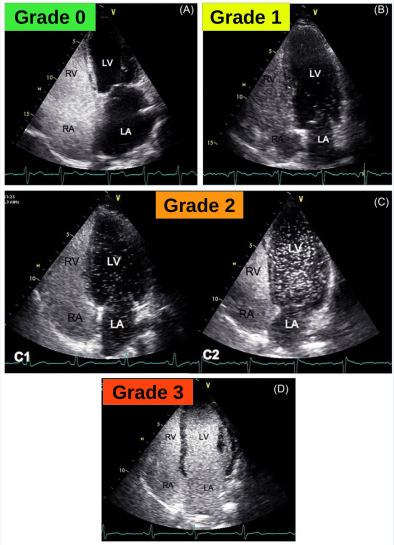
Control and therapy

- Decompression stops
- Recompression
- Gas breathed: oxygen

Introduction: Biomarker of individual response to decompression.

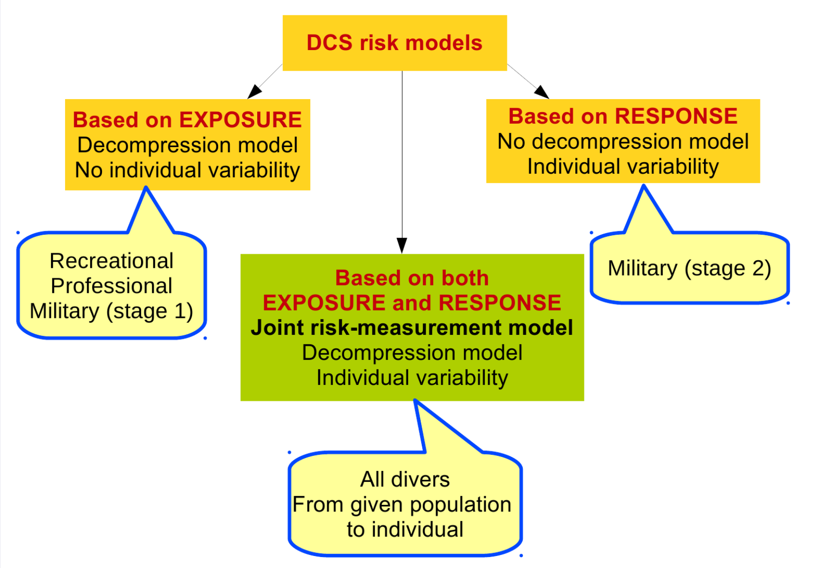
Biomarker of individual response to decompression: bubble grade measure

- Bubble monitoring:
  - oral by Doppler ultrasound
  - visual 2D echocardiography
- Clinical measure is made by specialist.
- Strongly quantized: grade $G \in \{0, 1, 2, 3, 4\}$.



Introduction: two competing classical approaches to DCS risk prediction

Three approaches to DCS risk modeling



Introduction: two competing classical approaches to DCS risk prediction

DCS prediction based on **exposure** (Weathersby & al.1991)

- **Pr(DCS | dive profile P) = function(Pt)**, where Pt is a gas pressure in tissues.
- Binary event (logistic) or time-to-event (linear hazard) risk models.
- Multi-compartiment(up to 16) model

  dive profile P → *model* → **tissues gas pressure Pt**.
- Divers are copies of «standard diver».

Drawbacks: **Ingore the individual variabilty, can underestimate the risk.**

DCS prediction based on **response** (Eftedal & al.2007)

- **Pr(DCS | grade G) = function(G)** where G is the maximal observed individual bubble grade measure.
- Divers are different.
- Conditional independence Pr(DCS | G,P) = Pr(DCS | G).
- Risk in population

  Pr(DCS | dive profile P)=∑Pr(DCS | G) Pr(G | P)

  is based on grades statistics Pr(G | P) for the profile P.

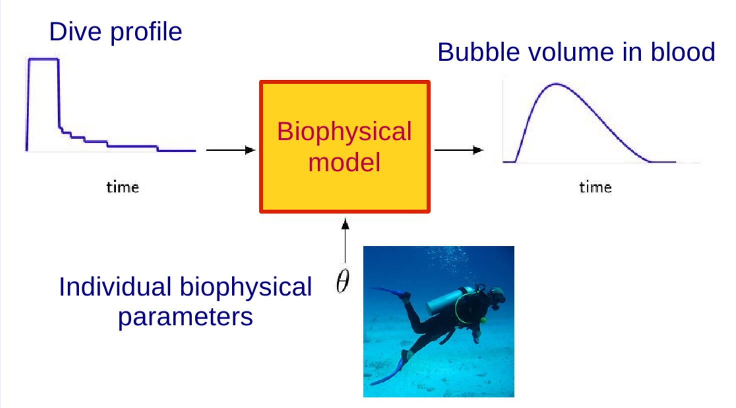
Drawbacks: **Unstable prediction** (grades depend on measurement time), **needs many dives** (to estimate Pr(G | P)).

Main model:Individual risk model for DCS.

Individual biophysical model of bubble formation (2010 J. Hugon)

- Nonlinear multi-compartiment model.
- Divers are different: individual biophysical parameters $\theta \in \Theta$
- In population: θ are i.i.d. of law π_θ

Evolution of bubble volume in blood $V(t) = V(t, P, \theta)$



Main model:Individual risk model for DCS.

Hazard model of individual risk of DCS

For a given dive profile P and biophysical parameters θ: the DCS is described by hazard model with intensity $\beta_1 h(V(s,P,\theta)$ and pure hazard component β_0:

$$\text{Pr(DCS before t | P,}\theta) = \beta_0 + 1 - \exp\left(-\beta_1 \int_0^t h(V(s,P,\theta))ds\right)$$

where $\beta_1 > 0$ and $0 < \beta_0 < \exp\left(-\beta_1 \int_0^T h(V(s,P,\theta))ds\right)$, $h(v) \geq 0$ is known function that defines relevant time-dependent features of bubble volume.

Risk of DCS in population

For a given dive profile P and a distribution π_θ of parameters θ in population:

- Mean probability of DCS in population:

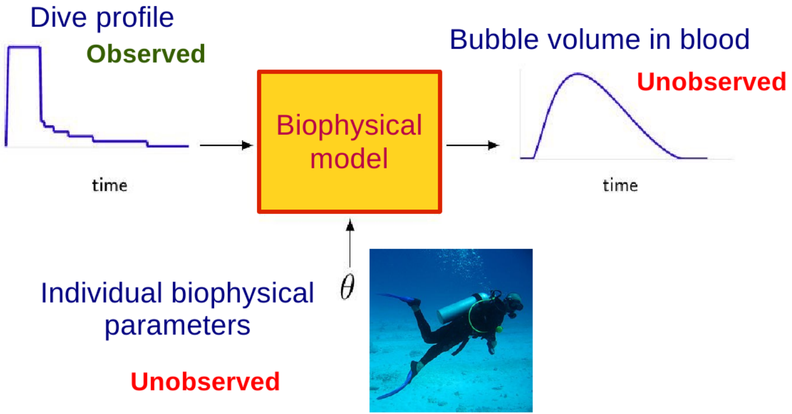
$$\text{Pr(DCS | P)} = \mathbb{E}_{\pi_\theta}\text{Pr(DCS | P,}\theta).$$

- Distribution of probabilities of DCS in population:

$$(\text{Pr(DCS | P,}\theta),\ \theta \sim \pi_\theta).$$

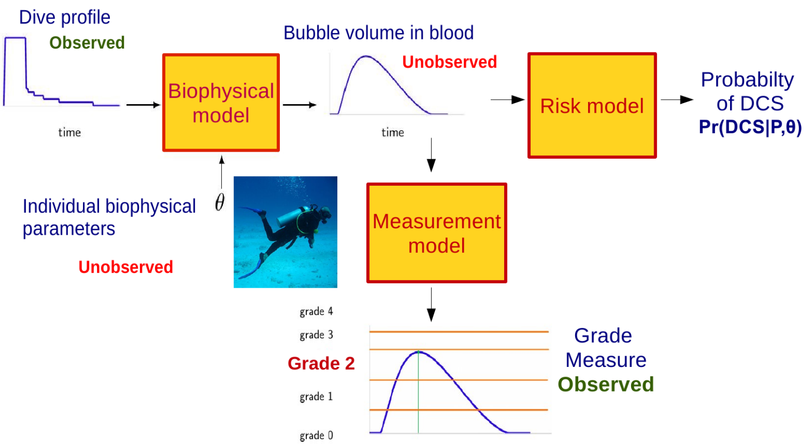
Main model: Joint risk-measurement model.

Observability problem



Main model: Joint risk-measurement model.

Solution: Joint risk-measurement model



Main model: Joint risk-measurement model.

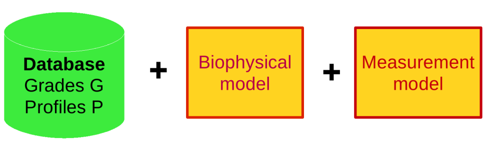
Measurement model for grades

Grade measure $G(P,\theta)$ is supposed to be treshold transformation of $\max_{t\in[0,T]} V(t,P,\theta)$:

$$\forall G \in \{0,1,2,3,4\} \qquad G(P,\theta) = G \iff \max_{t\in[0,T]} V(t;P,\theta) \in [\tau_G, \tau_{G+1}]$$

Thresholds $\tau = (\tau_1, \tau_2, \tau_3, \tau_4), \tau_G < \tau_{G+1}$, are supposed to be known.

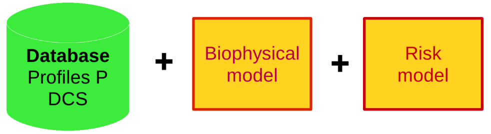
Distribution of individual parameters π_θ



(Y. Bennani & al. 2015) Continuous, non-gaussian distribution $\hat{\pi}_\theta$ is estimated on a compact set $\Theta \subset \mathbb{R}^2$ using nonparametric methods.
We assume π_θ is known and equal $\hat{\pi}_\theta$.

Main model. Results: simulations and real data.

Database for risk estimation



- 131 standard mititary dive profiles P_k
- N=53215 dives, A=24 accidents (DCS rate 0.045%)
- Highely unballanced data: dangerous profiles are much less used.

Considered model

Linear hazard model with "total volume features"

$$\Pr(\mathrm{DCS}|P,\theta) = \beta_0 + 1 - \exp\left(-\beta_1 \int_0^T V(t,P,\theta)dt\right), \quad \beta = (\beta_0, \beta_1) \in \mathcal{B} \in \mathbb{R}^2.$$

We consider the data as being generated by a Cox process with random intensity $\beta_1 V(t,P,\theta)$, that depends on a couple (P_k, θ) with known P_k's and θ randomly distributed according π_θ.

Main model. Results: simulations and real data

Maximum Likelihood Estimation of parameters

We estimate $\beta \in \mathcal{B} \subset \mathbb{R}^d$ by the maximum of (log-)likelihood:

$$\hat{\beta} = \arg\max_{\beta \in \mathcal{B}} LL_{(A_k, N_k, P_k)_{k=1}^K}(\beta)$$

where the loglikelihood is:

$$LL_{(A_k, N_k, P_k)_{k=1}^K}(\beta) \propto \sum_{k=1}^{K} (A_k \ln(\mathbb{E}_{\pi_\theta} \Pr(\text{DCS} \mid P_k, \theta)) + (N_k - A_k) \ln(1 - \mathbb{E}_{\pi_\theta} \Pr(\text{DCS} \mid P_k))$$

and A_k is the number of DCS within N_k dives with profile P_k.

Numerical challenges

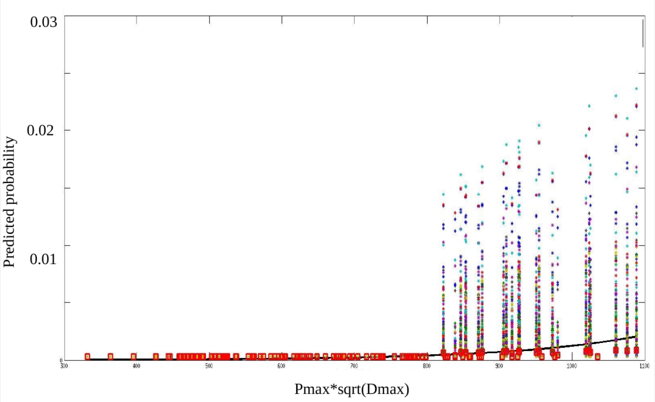
1. For 131 profiles P_k, we need 131 s to compute $V(t, P_k, \theta)$ for one θ.
   - Monte-Carlo sampling from π_θ.
   - Gaussian process interpolation $\int_0^T V(t, P_k, \theta) dt \sim \mathcal{GP}(\mu_k, K_k(\theta, \theta'))$ with respect to θ using the Best Linear Predition. We learn 131 kriging models.
2. The distribution of estimators is not guarateed to be close to asymptotic normal law. So we use the parametric bootstrap methods for confidence bounds.

Main model. Results: simulations and real data.

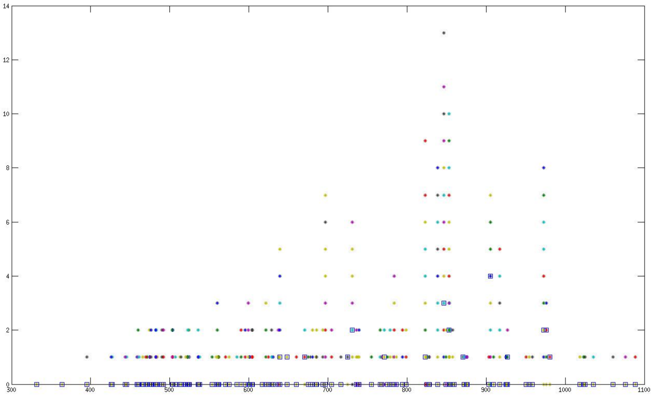
Results obtained on real data

- We succeded in parameter estimation. The loss in loglikelihood was 30 points wrt $\mathcal{B}(P_k, p_k)$ model.

Distribution of predicted individual probabilities



Illustrations: real data and data simulated by parametric bootstrap



Results obtained in simulations

- Estimators are not in asymptotic gaussian regime. But the the mean of bootstrap distribution of estimators is close to estimated value.
- Scaling simulation: $N_k^\lambda = \lambda \cdot N_k$. For $\lambda = 10$ we are already close to asymptotic regime. For $\lambda = 100$ the asymptotic normal regime is attained for estimators and for loglikelihoods.

Asymptotic formulas

Convergence of estimators: $\sqrt{\lambda}(\hat{\beta}_\lambda - \beta_{true}) \to \mathcal{N}(0, I^{-1}(\beta_{true}))$ with

$$I(\beta_{true}) = \sum_{k=1}^{K} N_k f_k^t(\beta_{true}) f_k(\beta_{true}), \quad f_k(\beta_{true}) = \frac{1}{\sqrt{p_{\beta_{true}}(P_k)(1 - p_{\beta_{true}}(P_k))}} \nabla_\beta p_{\beta_{true}}(P_k).$$

Convergence of loglikelihood: $\sqrt{\lambda}\left(\frac{LL(\beta_\lambda)}{\lambda} - H(\beta_{true})\right) \to \mathcal{N}(0, \Sigma(\beta_{true}))$ with

$$H(\beta_{true}) = \sum_{k=1}^{K} N_k \left(p_{\beta_{true}}(P_k) \ln p_{\beta_{true}}(P_k) + (1 - p_{\beta_{true}}(P_k)) \ln(1 - p_{\beta_{true}}(P_k))\right)$$

$$\Sigma(\beta_{true}) = \sum_{k=1}^{K} N_k \Sigma_k(\beta_{true}), \quad \Sigma_k(\beta_{true}) = p_{\beta_{true}}(P_k)(1 - p_{\beta_{true}}(P_k)) \cdot \ln^2\left(\frac{p_{\beta_{true}}(P_k)}{1 - p_{\beta_{true}}(P_k)}\right)$$

Discussion

Conclusions

- Estimation procedure work well.
- Model reproduces the variability in DCS exposure.
- We cannot replace the divers by a “standard diver”.
- Model selection and testing is complicated : rare data and multiple testing problem.

Perspectives

- Apply our approach to the data with grades measures and more DCS (first results are very encouraging).
- Get DCS time data in order to check the predicted risk evolution with time
- Introduce covariates: PFO (with size), obsesity....
- Design of experience (dive profiles to be tested) to optimize the model estimation.
- Learn the bubble volume signal forms to simplify computations.
- For testing: introduced metric on the dive profiles set.
- Individualise predictions: use multiple longitudinal bubble grade measures.
- Classify the divers into risk groups, compute class-conditioned predictions.

Thank you for your attention!

Questions?