Parameter estimation of a tuberculosis model in a patchy environment in Cameroon

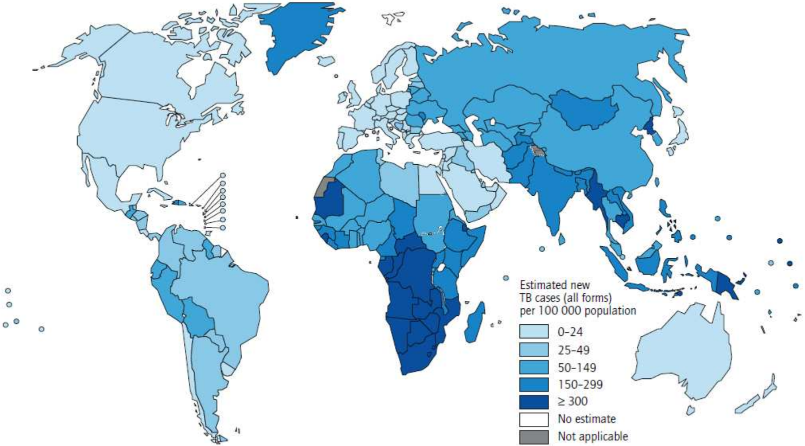
D. P. Moualeu

Joint work with S. Bowong, J. Kurths, P. Deuflhard

Biomat Conference 2013

Toronto, November 4, 2013

TB distribution 2012



[WHO, 2012]

Tuberculosis in Cameroon

Source: [*vidiani.com/maps*]

TB Notification 2011

- New pulmonary TB Cases: 19868
- Men 15-54 years old: 40%
- Women 15-54 years old: 51.54%
- HIV test positive: 38.91%
- Newly enrolled in HIV cases: 36458

TB Outcome 2010

- New pulmonary smear-positive cases cured: 63.97%
- New pulmonary smear-positive cases died: 5.66%
- Quitting treatment: 9.16%

TB Estimations in 2011 (for 100,000 population)

- Estimated incidence of TB: 243
- Estimated HIV in TB incidence: 76
- Estimated number of deaths from TB : 24
- Estimated Prevalence of deaths from TB : 299

Source: [*who.int/tb/country/en/*]

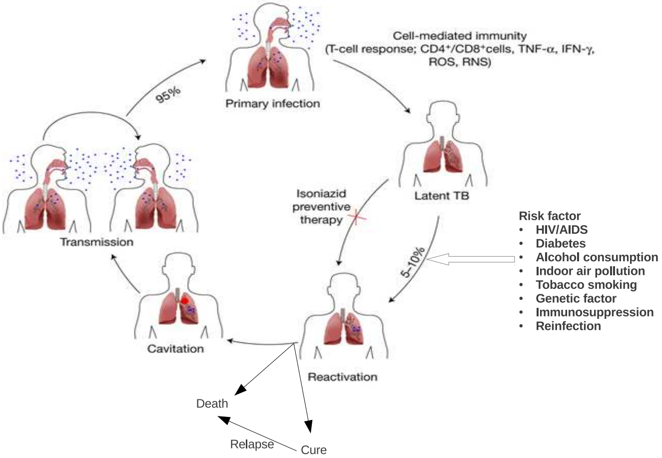
Aims

- A model for transmission dynamics of TB among Cameroon's regions
- Parameter identification of the model

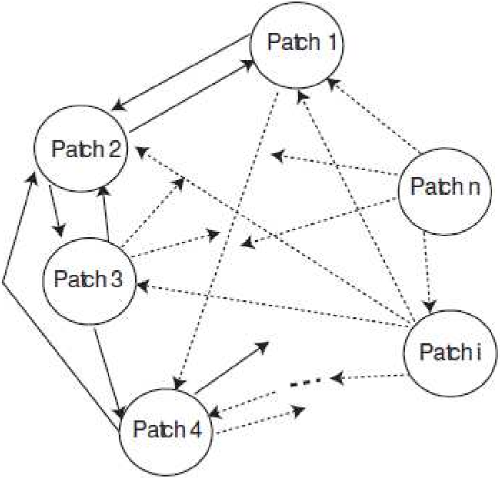
What can we use such model for?

- Explore the role of undiagnosed infectious on TB transmission
- Identify key parameters on TB dynamics
- Determine sensitivities to changes in parameter values
- Estimate key parameters from measurable data

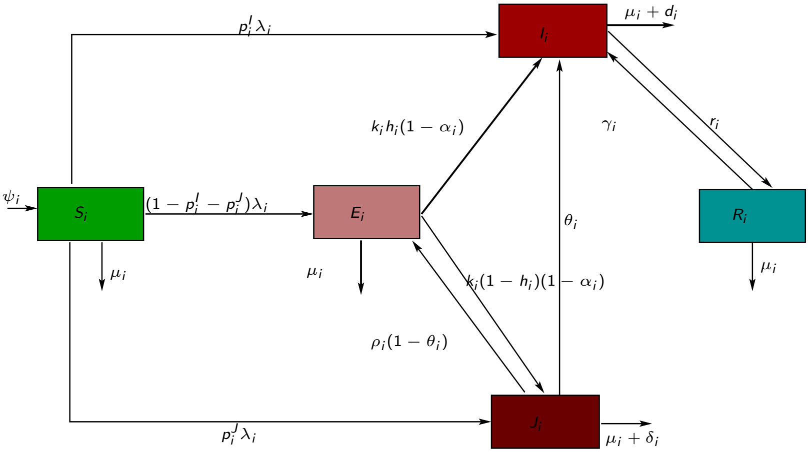
TB life cycle



Migration model



Components and compartments



Differential equations

Force of infection: $\lambda_i = \beta_i^I \dfrac{I_i}{N_i} + \beta_i^J J_i,$

Model

$$
\begin{cases}
\dot{S} &= \psi - \lambda \cdot S - \mu S + \mathcal{M} S \\
\dot{E} &= (\mathbf{1} - p^I - p^J) \cdot \lambda \cdot S + \rho \cdot (\mathbf{1} - \theta))J - A_E \cdot E + \mathcal{M} E \\
\dot{I} &= p^I \cdot \lambda \cdot S + \theta \cdot J + \gamma \cdot R + h \cdot (\mathbf{1} - \alpha) \cdot k \cdot E - A_I) \cdot I + \eta \mathcal{M} I \\
\dot{J} &= p^J \cdot \lambda \cdot S + (\mathbf{1} - h) \cdot (\mathbf{1} - \alpha) \cdot k \cdot E - A_J \cdot J + \eta \mathcal{M} J \\
\dot{R} &= r \cdot I - A_R \cdot R + \mathcal{M} R
\end{cases}
$$

Basic reproduction ratio

$$\begin{cases} \dot{x} &= \varphi(x) + \mathcal{M}S - \lambda(I)x, \\ \dot{y} &= \mathcal{F}(x,y) - \mathcal{V}(x,y), \end{cases}$$

where $x = S \in \mathbb{R}^n$ and $y = (E, I, J, R) \in \mathbb{R}^{4n}$.

$$\mathcal{R}_0 = \rho(\mathcal{F}_y(x_0, 0) \cdot (\mathcal{V}_y(x_0, 0))^{-1})$$

- Basic reproduction ratio ($\mathcal{R}_0$): number of active cases one infectious generates on average over the course of its infectious period
- $\mathcal{R}_0 \leq 1$: TB dies out in the long run
- $\mathcal{R}_0 > 1$: TB persists and spread

Parameter dependent model

- Model
$$\frac{d}{dt}y(t,\mathbf{p}) = f(t,y,\mathbf{p}), \qquad t \geq 0$$
- Initial states vector $y(0,\mathbf{p}) = y_0 \in \mathbb{R}^N$
- Vector of parameters $\mathbf{p} \in \mathbb{R}^q$

Sensitivity analysis

$$\mathbf{S}_{ij}(t) := \left(\frac{\partial y_i}{\partial \mathbf{p}_j}(t)\right), \qquad i = 1, \cdots, N, \;\; j = 1, \cdots, q$$

$$\mathbf{S}' = f_y(y, \mathbf{p})\mathbf{S} + f_{\mathbf{p}}(y, \mathbf{p}), \qquad \mathbf{S}(t_0) = 0$$

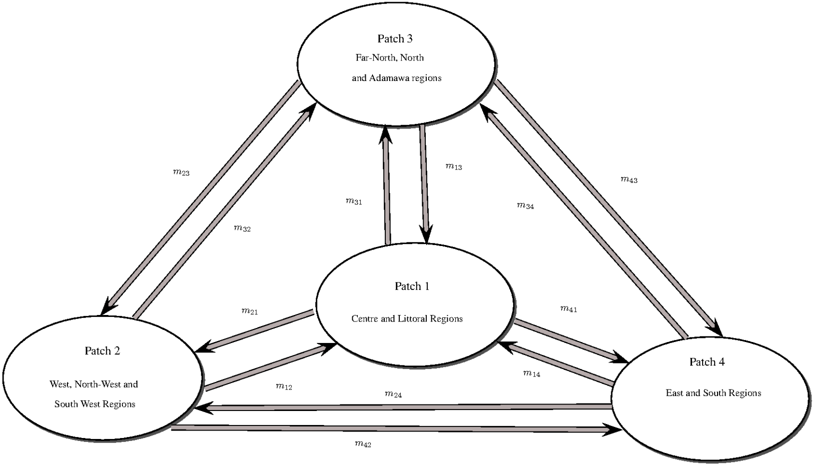
- Analysis of $\mathbf{S}$:

$$\mathbf{S}_j(t_k) := (\mathbf{S}_{1j}(t_k), \cdots, \mathbf{S}_{nj}(t_k))^T$$

$$\mathbf{S}_{ij}(t_k) = \left(\frac{\partial y_{k_i}(t_k, \mathbf{p})}{\partial \mathbf{p}_j}\right), \quad k_i = 1, \cdots, N$$

- Small sensitivity norms $\|\mathbf{S}_j\| = \|(\mathbf{S}_{ij}(t)\|, \quad i = 1, \cdots m$ indicate a small sensitivity

Application on 4 patches



Sensitivity analysis (results)

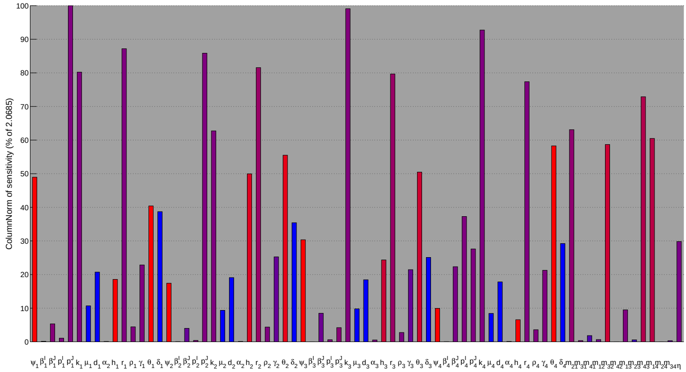
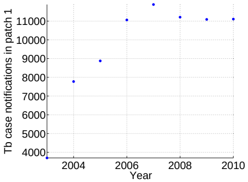
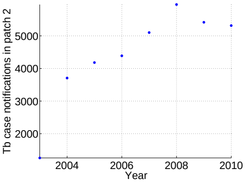


Figure: Sensitivity norms of unknown parameters

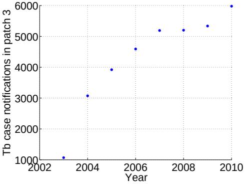
Data: number of diagnosed infectious



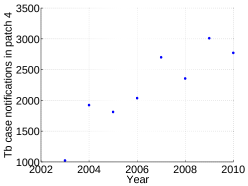
(a) I_1



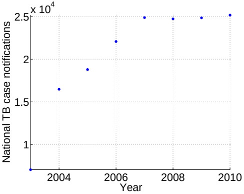
(b) I_2



(c) I_3

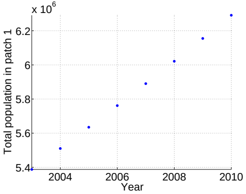


(d) I_4

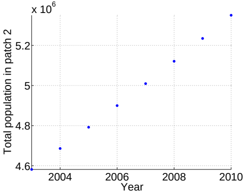


(e) I

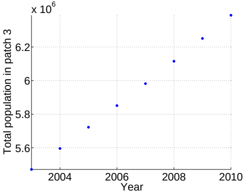
Data: total population



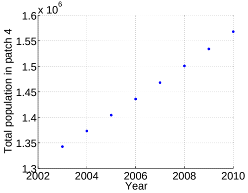
(f) N_1



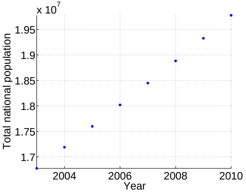
(g) N_2



(h) N_3



(i) N_4



(j) N

Nonlinear least-square problem

- Least squares formulation

$$\|F(\mathbf{p})\|_2^2 = \frac{1}{m}\sum_{j=1}^{m}\left\|\frac{y(\tau_j,\mathbf{p}) - z_j}{\delta z_j}\right\|_2^2 \longrightarrow min$$

- Data $z = (z_1, \cdots, z_m)$
- δz_i : measurement accuracy of z_i
- The relative measurement accuracy is $\delta z_i = \varepsilon_z z_i$ with $\varepsilon_z = 10^{-1}$ to 10^{-3} in experiments

Gauss-Newton algorithm

- Solution of the nonlinear least squares problem by a global adaptive Gauss-Newton method

$$\| F'(\mathbf{p}^k) \cdot \Delta \mathbf{p}^k + F(\mathbf{p}^k) \|_2^2 \longrightarrow \min, \\ \mathbf{p}^{k+1} = \mathbf{p}^k + \lambda_k \Delta \mathbf{p}^k, \quad k = 0, 1, 2, \ldots$$

[P. Deuflhard: Newton Methods for Nonlinear Problems, 2004]

- Sequence of linear least squares problems with $(m \times q)$ Jacobian matrix $F'(\mathbf{p})$
- A closer look of the expression of $F'(\mathbf{p})$ reveals that

$$F'(p) = \left(\frac{1}{\delta z_j} \right) \mathcal{S}, \qquad \mathcal{S} = (\mathbf{S}(t_1), \cdots, \mathbf{S}(t_m))$$

- **Good initial guess** required

Identifiability

- QR factorization with column pivoting

$$F'(\mathbf{p}^k)\Pi = QR, r_{11} \geq r_{22} \geq \cdots \geq r_{qq}$$

[P. Deuflhard and A. Hohmann,2003]

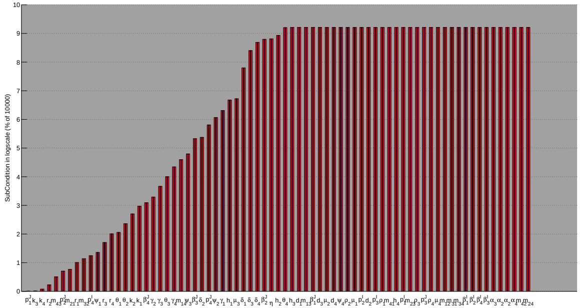
- The sub-condition of parameter $\mathbf{p}_j$ is defined by

$$sc_j = \frac{r_{11}}{r_{jj}}$$

- Identifiable parameters: $\varepsilon_{\mathbf{p}_j} sc_j < 1$

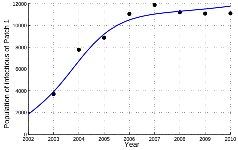
[P. Deuflhard and Sautter,1980]

Identifiability (results)

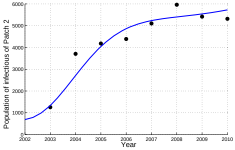


- Dependencies between parameters
- Only a few parameters can be identified

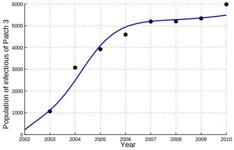
Numerical results (I)



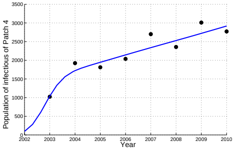
(k) I_1



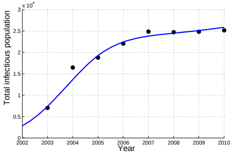
(l) I_2



(m) I_3

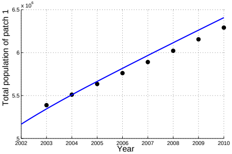


(n) I_4

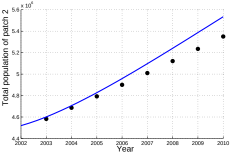


(o) I

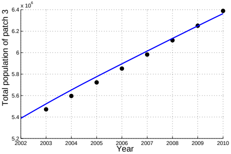
Numerical results (N)



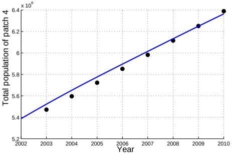
(p) N_1



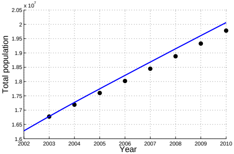
(q) N_2



(r) N_3

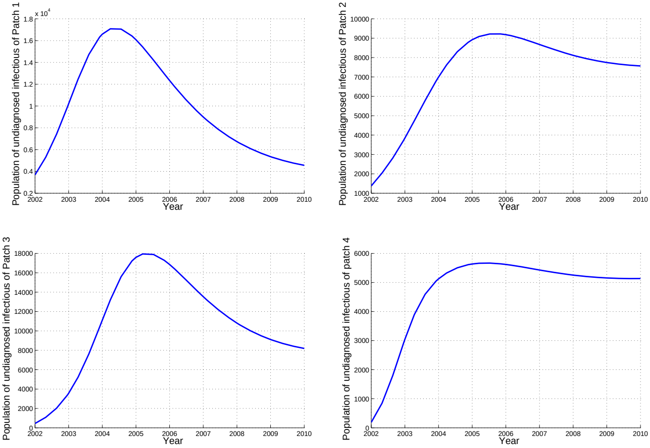


(s) N_4

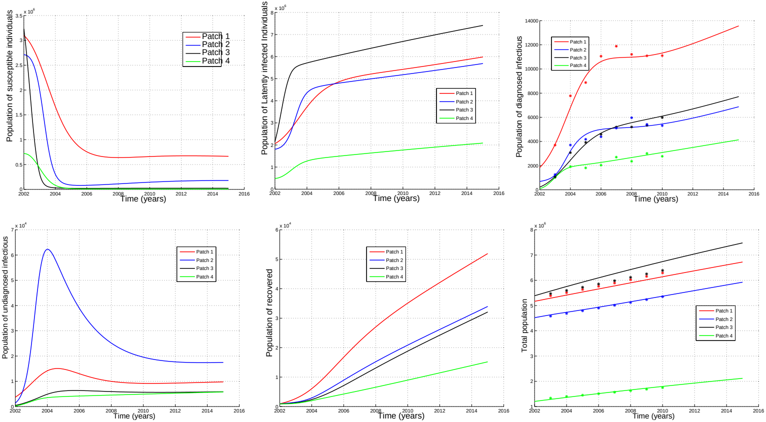


(t) N

Numerical results (J)



Numerical results (J)



Acknowledgements

- Prof. Peter Deuflhard
- Dr. Samuel Bowong
- Dr. Susanna Röblitz
- Dr. Martin Weiser
- Dr. Rainald Ehrig
- Prof. Jürgen Kurths

Berlin Mathematical School

ZIB

BMS

Zuse Institute Berlin
Computational Systems Biology Group
http://www.zib.de/Numerik/CompSysBio/index.en.html