OPTIMAL RESOURCE ALLOCATION FOR HIV PREVENTION AND CONTROL

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Outline

Motivation for research

Public health challenges:

- Determine the public-level efficacy of various intervention programs.
- Describe the transmission dynamics of a disease and the effect of intervention using a model of the underlying medical, biological, and social processes.
- Perform effective triage of limited prevention resources.

Motivation for research

Current state:

- Analytical or semi-analytical methods for computing optimal control profiles for simple epidemiological models.
  - (–) Obtained results are typically not suitable for practical use; too restrictive modeling assumptions.
- Commercial tools aimed at high-level decision-makers for choosing the best public health investments: OPTIMA, etc.
  - (–) A *one–size–fits–all* approach leads to solutions that lack relevant details or specific constraints.

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  (–) A *one–size–fits–all* approach leads to solutions that lack relevant details or specific constraints.

Motivation for research

What we offer:

- Population balance models tailored to particular applications.
- Realistic model of different prevention/treatment programs.
- Consider hard constraints.
- Locally defined cost functions expressed in $$$.
- Integrate the obtained results into epidemiological practice by providing programmatic benchmarks.
- Allow a practitioner to draw concrete conclusions about optimal resource allocation in a specific setting.

Population balance models

- Total population is separated in a number of *compartments*.
- Compartment: a *homogeneous* subgroup of the population.
- *Dynamics*: transitions between groups and the in- and out-flows.

The dynamics of the ith compartment's population:

$$\dot{x}_i = \sum_{i \neq j} \left(a_{ij}(x) - a_{ji}(x) \right) - a_{ii}(x) + w_i,$$

where
x_i – the number of individuals within ith compartment,
a_{ji} – the flow rate from compartment i to compartment j,
a_{ii} – the outflow out of the ith compartment, and
w_i – the inflow into the ith compartment.

(A)

1. $a_{ij}(x) \geq 0$ and $w_i \geq 0$ for all i, j and $x \in \mathbb{R}^n_{\geq 0}$.
2. $x_i = 0$ implies $a_{ji}(x) = 0$ and $a_{ii}(x) = 0$, i.e. there is no flow out of an empty compartment.

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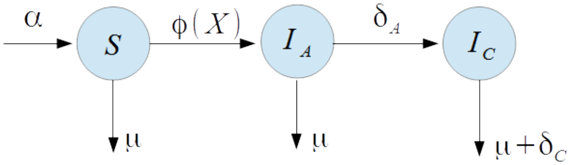
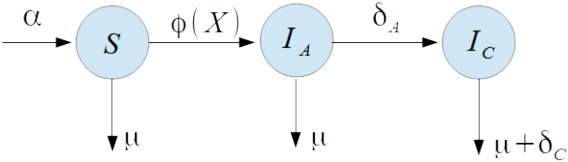
An example

Consider a population divided into 3 compartments:
S – *susceptible*, I_A – *acutely infected*, and I_C – *chronically infected*.



where
α – the inflow,
μ – the mortality,
δ_A – (duration of the acute phase)$^{-1}$,
$\phi(X)$ – the incidence rate.

An example: the model

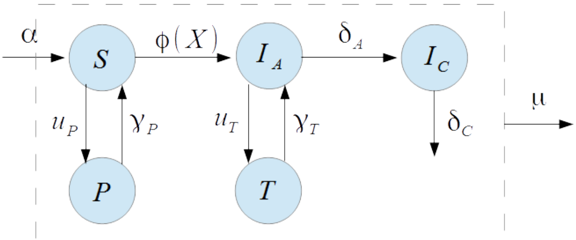


$$\begin{aligned}
\dot{I}_A &= \phi(X)S - (\delta_A + \mu)\, I_A \\
\dot{I}_C &= \delta_A I_A - (\delta_C + \mu)\, I_C \\
\dot{S} &= \alpha - (\mu + \phi(X))\, S,
\end{aligned}$$

where $\phi(X) = \dfrac{\beta_A I_A + \beta_C I_C}{N}$, $X = [I_A,\, I_C,\, S]$, and $N = S + I_A + I_C$.

An example: controlled case

Add 2 more compartments: T – *treatment*, P – *prophylaxis*.



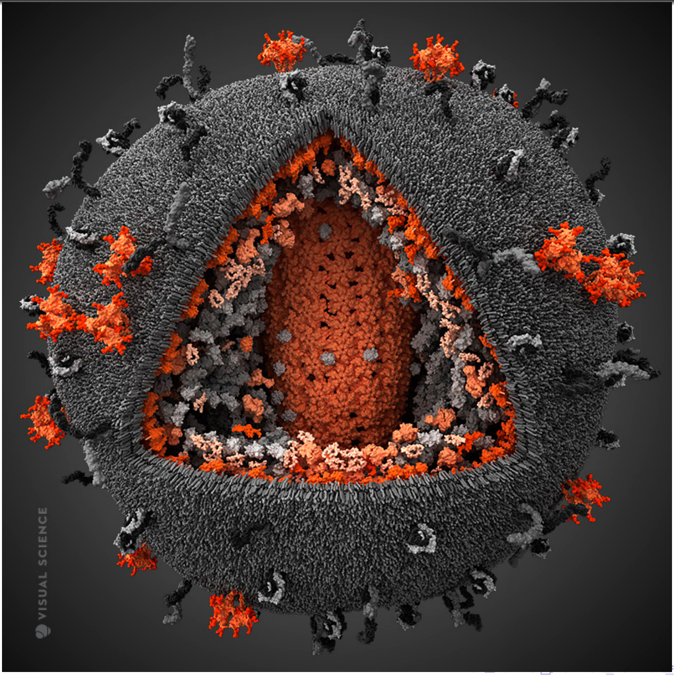
$$
\begin{aligned}
\dot{I}_A &= \phi(X)S - (\delta_A + \mu)\, I_A \\
\dot{I}_C &= \delta_A I_A - u_T I_C + \gamma_T T - (\delta_C + \mu)\, I_C \\
\dot{S} &= \alpha - (\mu + \phi(X))\, S + \gamma_P P - u_P S \\
\dot{T} &= u_T I_C - (\mu + \gamma_T)\, T \\
\dot{P} &= u_P S - (\mu + \gamma_P)\, P,
\end{aligned}
$$

where u_T and u_P – fractions of the respective populations that are addressed; γ_T and γ_P – the rates at which the prescribed care fails.

An example: control theoretic view point

$$\frac{d}{dt}\begin{bmatrix} I_A \\ I_C \\ S \\ T \\ P \end{bmatrix} = \begin{bmatrix} \phi(X)S - (\delta_A + \mu)\, I_A \\ \delta_A I_A + \gamma_T T - (\delta_C + \mu)\, I_C \\ \alpha - (\mu + \phi(X))\, S + \gamma_P P \\ -\,(\mu + \gamma_T)\, T \\ -\,(\mu + \gamma_P)\, P \end{bmatrix} + \begin{bmatrix} -I_A & 0 \\ 0 & 0 \\ 0 & -S \\ I_A & 0 \\ 0 & S \end{bmatrix} \begin{bmatrix} u_T \\ u_P \end{bmatrix}$$

- A bilinear control system.
- The system is not controllable in the neighborhood of X_{DFE}.
- $\dim(\text{controllable subspace}) = 1$!
- $R_0 > 1 \Rightarrow$ uncontrollable subspace is unstable $\rightsquigarrow$ system is not stabilizable.
- Standard non-linear control methods are not applicable ...


VISUAL SCIENCE

HIV Transmission: intro

- Sexually transmitted diseases are particularly suitable for modeling.
- Further specialization of the model: **M**en having **S**ex with **M**en.
- Gay population in USA: 3-4% of total population $\rightsquigarrow$ 60-70% new infections
- Compartmental model: 9 subpopulations (2 x Susceptible, 4 x Infected, 2 x Treatment, 1 x Prophylaxis)
- 2 controls: TaP vs. PrEP (fractions of screened individuals that are administered either to treatment or to prophylaxis)

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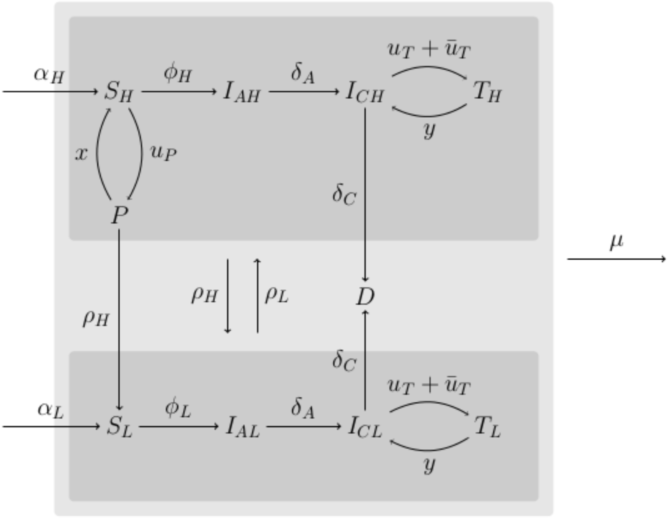
HIV Transmission: compartmental model



HIV Transmission: ODEs

$$
\begin{aligned}
\dot{S}_H &= \alpha_H - (\phi_H(X) + \rho_H + \mu)S_H + \rho_L S_L + xP - u_P\zeta_P(X)N \\
\dot{S}_L &= \alpha_L - (\phi_L(X) + \rho_L + \mu)S_L + \rho_H(S_H + P) \\
\dot{I}_{CH} &= \delta_A I_{AH} - (\rho_H + \mu + \delta_C + v_b)I_{CH} + \rho_L I_{CL} + yT_H - u_T\zeta_{T,H}(X)N \\
\dot{I}_{CL} &= \delta_A I_{AL} - (\rho_L + \mu + \delta_C + v_b)I_{CL} + \rho_H I_{CH} + yT_L - u_T\zeta_{T,L}(X)N \\
\dot{I}_{AH} &= \phi_H S_H - (\rho_H + \mu + \delta_A)I_{AH} + \rho_L I_{AL} \\
\dot{I}_{AL} &= \phi_L S_L - (\rho_L + \mu + \delta_A)I_{AL} + \rho_H I_{AH} \\
\dot{T}_H &= -(y + \rho_H + \mu)T_H + v_b I_{CH} + \rho_L T_L + u_T\zeta_{T,H}(X)N \\
\dot{T}_L &= -(y + \rho_L + \mu)T_L + v_b I_{CL} + \rho_H T_H + u_T\zeta_{T,L}(X)N \\
\dot{P} &= -(x + \rho_H + \mu)P + u_P\zeta_P(X)N,
\end{aligned}
$$

where $\zeta_{(*)}(X)$ and $\phi_{(*)}(X)$ are rational functions related to probabilities.

Optimal control problem

- Consider the period $[0, t_f]$ divided into n_{int} equal intervals
- Over each single interval i the control is constant: $U^i = [u_T^i,\ u_P^i] \in \mathbb{R}^2$
- Minimize the total incidence rate:

$$J^C(X) = \int_0^{t_f} S_H \phi_H(X) + S_L \phi_L(X) dt,$$

- Budgetary restrictions (for each interval $[t_{i-1}, t_i]$):

$$J_i^B(X, U^i) =$$

$$= \int_{t_{i-1}}^{t_i} K_3[T_H(t) + T_L(t)] + K_4 P(t) + K_5 N(t) u_T^i(t) + K_6 N(t) u_P^i(t) ds,$$

and

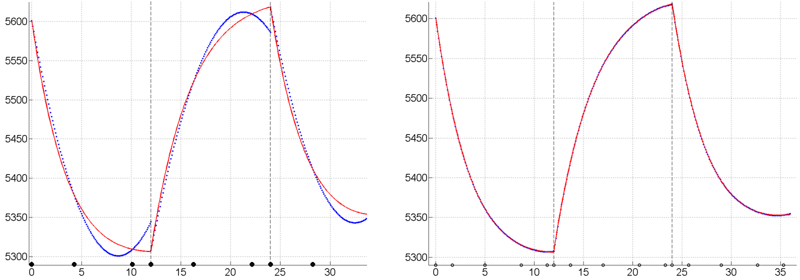
$$J_i^B(X, U^i) - J_i^B(\tilde{X}_i, \mathbf{0}) \leq B, \quad i = 1, \ldots, n_{int}.$$

Numerical approach

- The total interval is separated into n_{int} subintervals
- Over each interval the system's trajectory is interpolated by Lagrange polynomials with a non-uniform grid $\{\tau_i\}_{i=0}^{n_{cp}}$.

$$\hat{X}_j(t) = \sum_{k=0}^{n_{cp}} L_k(t) X_j(\tau_k), \text{ where } L_k(t) = \prod_{l=0,\, l\neq k}^{n_{cp}} \frac{t-\tau_l}{\tau_k-\tau_l}.$$

- The trajectory (solution) is parametrized by $X_j(\tau_k)$.
- Grid points – zeros of a Legendre/Chebyshev polynomial (recall Runge's phenomenon)



Numerical approach (cont'd)

- *Integration and differentiation reduce to linear algebraic operations*

  Differentiating $\hat{X}_j(t) = \sum_{k=0}^{n_{cp}} L_k(t) X_j(\tau_k)$ and evaluating at τ_k we get

$$\dot{\hat{X}}_j(\tau_k) = \sum_{l=0}^{n_{cp}} X_j(\tau_l) \dot{L}_l(\tau_k) = \sum_{l=0}^{n_{cp}} X_j(\tau_l) D_{kl},$$

  where D is an $[n_{cp} \times (n_{cp}+1)]$ *differentiation matrix.*

- *DEs* $\dot{X} = F(X, U)$ *turn into a set of linear algebraic equations*:

$$D\mathbf{X} - \frac{\delta t}{2} F(\mathbf{X}, U) = 0,$$

  where $\mathbf{X}_{j,k} = X_j(\tau_k)$, and δt is the length of the interval.

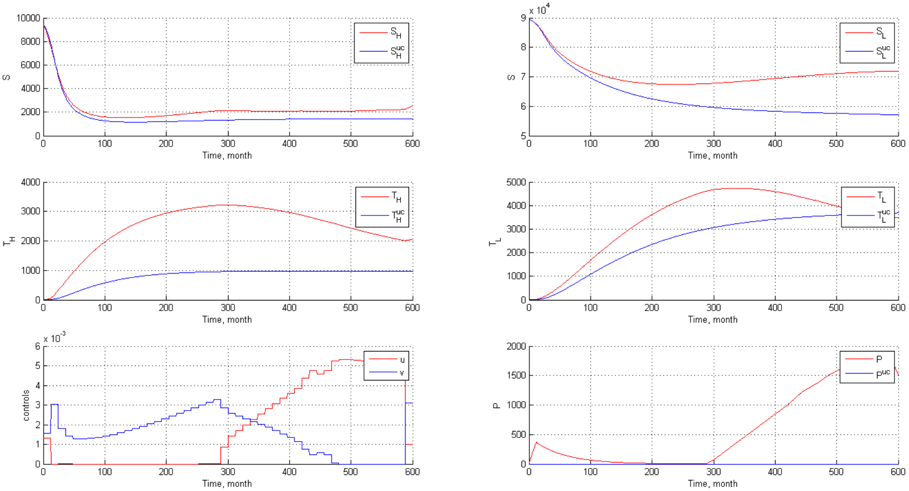
Numerical approach: what's at the end?

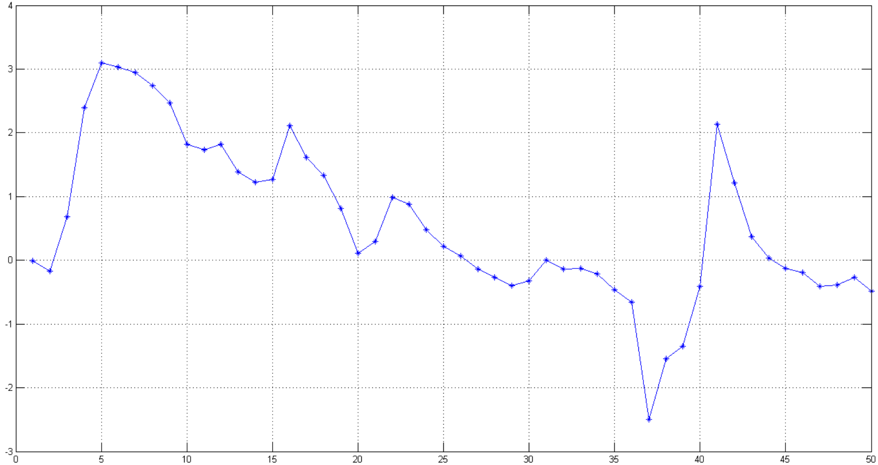
Resulting nonlinear constrained optimization problem:

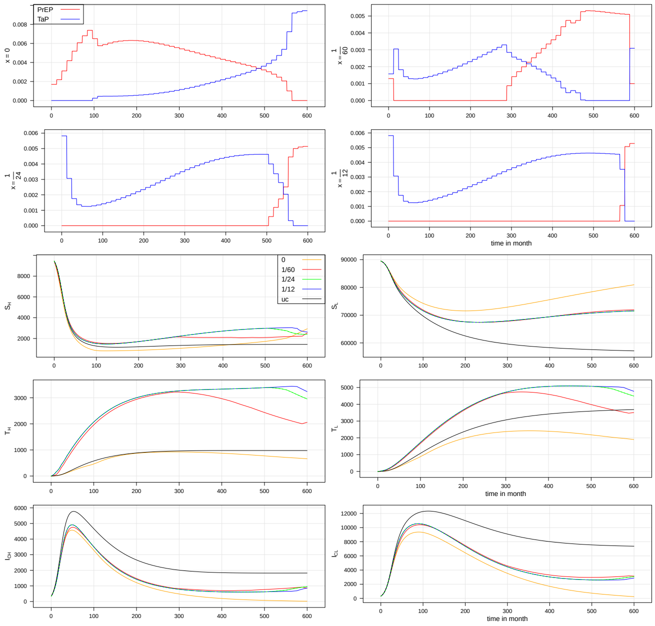
$$
\begin{cases}
\dfrac{\delta t}{2} \displaystyle\sum_{i=1}^{n_{int}} \sum_{k=0}^{n_{cp}} w_k C(\mathbf{X}(\tau_k^i), U^i) \to \min \\
\text{s.t. } D\mathbf{X}^i - \dfrac{\delta t}{2} F(\mathbf{X}^i, U^i) = 0 \\
\qquad X(\tau_0^i) - \dfrac{\delta t}{2} \displaystyle\sum_{k=0}^{n_{cp}} w_k F_j(\mathbf{X}(\tau_k^i), U^i) = 0, \; i = 1, \dots, n_{int}, \\
\qquad D\mathbf{X}_0^i - \dfrac{\delta t}{2} F(\mathbf{X}_0^i, 0) = 0, \qquad i = 1, \dots, n_{int}, \\
\qquad \mathbf{X}_0^i(t_{i-1}) = \mathbf{X}(t_{i-1}^i), \qquad i = 1, \dots, n_{int}, \\
\qquad \dfrac{\delta t}{2} \displaystyle\sum_{k=0}^{n_{cp}} w_k \left[B^i(\mathbf{X}^i(\tau_k^i), U^i) - B^i(\mathbf{X}_0^i(\tau_k^i), 0) \right] - B_{lim} \le 0, \\
\qquad\qquad i = 1, \dots, n_{int}.
\end{cases}
$$

Implementation

- The described problem is implemented in Matlab with `fmincon`.
- Computation time depends on the initial guess. Typically a couple of hours.
- Reason for large time consumption: sensitivity of the constraints to the control values.


S
Time, month
S_H
S_H^{uc}
x 10^4
S
Time, month
S_L
S_L^{uc}
T_H
Time, month
T_H
T_H^{uc}
T_L
Time, month
T_L
T_L^{uc}
x 10^{-3}
controls
Time, month
u
v
P
Time, month
P
P^{uc}


4
3
2
1
0
-1
-2
-3
0
5
10
15
20
25
30
35
40
45
50


PrEP
TaP
x = 0
$x = \frac{1}{60}$
$x = \frac{1}{24}$
$x = \frac{1}{12}$
time in month
0
1/60
1/24
1/12
uc
S_H
S_L
T_H
T_L
I_{CH}
I_{CL}
time in month
time in month

Suboptimal solutions

If one component of U^i is kept zero $\forall t \in [0, t_f]$, the optimization problem turns to a set of n_{int} scalar optimization problems:
Determine the value of control $U^i \in \{0\} \times \mathbb{R}_{\geq 0}$ ($U^i \in \mathbb{R}_{\geq 0} \times \{0\}$) s.t.

$$\begin{cases} \|U^i\| \to \max, \\ J_i^B(X, U^i) - J_i^B(\tilde{X}_i, \mathbf{0}) \leq B, \\ X(t),\ t \in [t_{i-1}, t_i], \\ \qquad \text{satisfies } (*) \text{ with } X(t_{i-1}) = X_{i-1} \text{ and } U(t) = U^i, \\ \tilde{X}_i(t),\ t \in [t_{i-1}, t_i] \\ \qquad \text{satisfies } (*) \text{ with } X(t_{i-1}) = X_{i-1} \text{ and } U(t) = 0, \end{cases}$$

which can be solved sequentially for $i = 1, \ldots, n_{int}$.

- Rule: determine the maximal value of the respective control such that the budgetary constraint holds.
- Scalar optimization problem: can be solved within seconds.

Suboptimal solutions (cont'd)

Suboptimal solutons

- can be computed for a large set of parameters;
- provide certain intuition about true optimal solutions:

	$x = 0$	$x = 1/60$	$x = 1/24$	$x = 1/12$
single TaP	6.843e+04	6.843e+04	6.843e+04	6.843e+04
single PrEP	4.179e+04	7.753e+04	8.852e+04	9.300e+04
mixed	4.109e+04	6.634e+04	6.829e+04	6.841e+04

Further analysis?

- Clusterization?
- Parallel coordinate plot.

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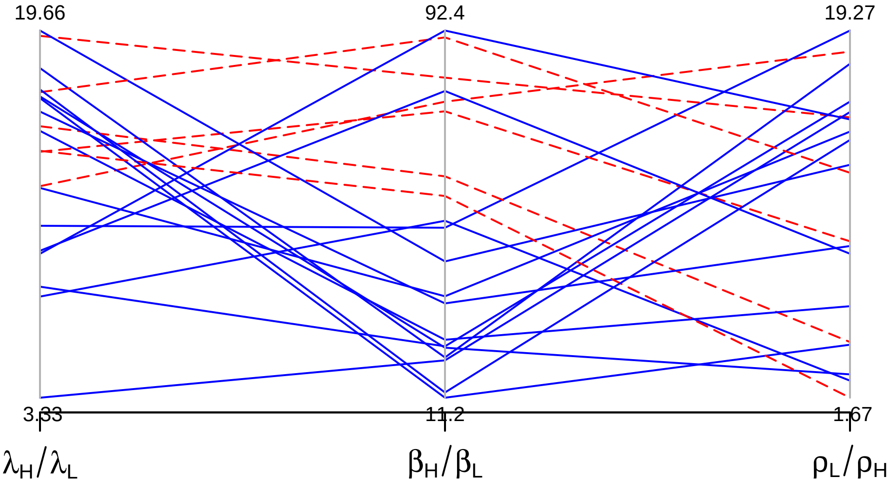
Parallel coordinate plot



We vary values of different param's, e.g. λ_H/λ_L, β_H/β_L, and ρ_L/ρ_H, and determine for each param. set if TaP or PrEP yields lower cost.

Enrollment

- Enrollment: by randomly sampling individuals at locations where high-risk individuals resp. chronically infected prevail (HRE).
- Evaluating probabilities using Bayes rule:

$$
\begin{aligned}
\mathrm{P}(X|\mathrm{HRE}) &= \frac{P(\mathrm{HRE}|R{=}H)P(X)}{P(\mathrm{HRE}|R{=}H)P(R{=}H)+P(\mathrm{HRE}|R{=}L)P(R{=}L)} \\
&= \frac{p_H\frac{X}{N}}{p_H\frac{N_H}{N}+p_L\frac{N_L}{N}} = \frac{r_bX}{r_bN_H+N_L},
\end{aligned}
$$

where $N_H{=}S_H{+}I_{AH}{+}I_{CH}{+}P{+}T_H$, $N_L{=}S_L{+}I_{AL}{+}I_{CL}{+}T_L$, $N{=}N_H{+}N_L$.

$r_b = p_H/p_L$ – odds of a high-risk person to go to a HRE.

State Estimation

- N_s – the number of individuals that were sampled at a HRE;
- $\hat{s}_{(\cdot)}, \hat{i}_{(\cdot)}, \ldots$ – fractions of the respective groups within the sample;
- Compute fractions of the respective groups within the total population:

$$\left[\begin{pmatrix} r_b\mathbf{I} & 0 \\ 0 & \mathbf{I} \end{pmatrix} + (1-r_b)\begin{pmatrix} \mathrm{diag}(\hat{x}_H) & 0 \\ 0 & \mathrm{diag}(\hat{x}_L) \end{pmatrix}\begin{pmatrix} \mathbf{1} & \mathbf{0} \\ \mathbf{1} & \mathbf{0} \end{pmatrix}\right]\begin{pmatrix} x_H \\ x_L \end{pmatrix} = \begin{pmatrix} \hat{x}_H \\ \hat{x}_L \end{pmatrix}$$

where $x_H = (s_H \quad i_{AH} \quad i_{CH} \quad t_H \quad p)^T$, $x_L = (s_L \quad i_{AL} \quad i_{CL})^T$ and a normalization condition $\sum \hat{x}_L + \sum \hat{x}_H = 1$ was employed.

State estimation (cont'd)

- Estimates for r_b.
- Some groups cannot be recognized during sampling, e.g., $S_H \leftrightarrow I_{AH}$.
- Statistical analysis: multinomial distributions.

  Not many results are available...
- "On-the-fly" state estimation.
- ...

Conclusions and future directions

Now:

- Efficient numerical optimization scheme
- A number of results aimed at providing practical rules for a decision maker

In future:

- Analyzing and addressing potential issues when applying the obtained results in epidemiological practice
- Application of control-theoretic methods to controlled population balance models.

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Work is in progress, we are open for suggestions and comments.

Thank you!