FORUM

Forum 1: BETTER, CHEAPER, FASTER: A REPORT ON THE SCIENCE OF OPTIMIZATION FROM THE ISPOR OPTIMIZATION TASK FORCE

6 November, 2017

ISPOR OPTIMIZATION METHODS EMERGING GOOD PRACTICES TASK FORCE

Optimization Methods in Health Care Delivery Task Force

Co-Chairs:

William Crown, PhD, Chief Scientific Officer, OptumLabs, Boston, MA, USA

Kal Pasupathy, PhD, Associate Professor, Health Systems Engineering, Mayo College of Medicine and
Scientific Director, Clinical Engineering Learning Lab, Mayo Clinic, Rochester, MN, USA

Task Force Members (1)

- **Nasuh Buyukkaramikli, PhD,** Scientific Researcher, institute of Medical Technology Assessment(iMTA), Erasmus University Rotterdam, the Netherlands
- **Maarten J. IJzerman, PhD**, Professor of Clinical Epidemiology & Health Technology Assessment (HTA); Head, Department of Health Technology & Services Research, University of Twente, Enschede, The Netherlands
- **Deborah A. Marshall, PhD,** Professor, Health Services Research and Health Economics, University of Calgary, Alberta, Canada
- **Alec Morton, PhD**, Professor of Management Science, University of Strathclyde, Glasgow, Scotland, UK

Task Force Members (2)

- **William V. Padula, PhD, MS**, Assistant Professor, Department of Health Policy & Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
- **Mustafa Sir, PhD**, Assistant Professor, Mayo College of Medicine, Rochester, MN, USA
- **Praveen Thokala, MASc, PhD,** Research Fellow, University of Sheffield, Sheffield, UK
- **Jon Tosh, PhD,** Consultant Health Economist, DRG Abacus, Manchester, UK
- **Peter Wong, PhD, MS, MBA, RPh**, Principal, Compass Clinical Consulting, Cincinnati, OH, USA

Optimization Task Force Report 1 – Introduction

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Constrained Optimization Methods in Health Services Research—An Introduction: Report 1 of the ISPOR Optimization Methods Emerging Good Practices Task Force

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William Crown, PhD[1,*], Nasuh Buyukkaramikli, PhD[2], Praveen Thokala, PhD[3], Alec Morton, PhD[4], Mustafa Y. Sir, PhD[5], Deborah A. Marshall, PhD[6,7], Jon Tosh, PhD[8], William V. Padula, PhD, MS[9], Maarten J. Ijzerman, PhD[10], Peter K. Wong, PhD, MS, MBA, RPh[11], Kalyan S. Pasupathy, PhD[12,*]

[1]OptumLabs, Boston, MA, USA; [2]Scientific Researcher, Institute of Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, The Netherlands; [3]Research Fellow, University of Sheffield, Sheffield, UK; [4]Professor of Management Science, Department of Management Science, Strathclyde Business School, University of Strathclyde, Glasgow, Scotland, UK; [5]Assistant Professor, Health Care Policy & Research, Information and Decision Engineering, Mayo Clinic Kern Center for the Science of Health Care Delivery, Rochester, MN, USA; [6]Canada Research Chair, Health Services & Systems Research; Arthur J.E. Child Chair in Rheumatology Research; Director, HTA, Alberta Bone & Joint Health Institute; [7]Associate Professor, Department Community Health Sciences, Faculty of Sciences, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada; [8]Senior Health Economist, DRG Abacus, Manchester, UK; [9]Assistant Professor, Department of Health Policy & Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [10]Professor of Clinical Epidemiology & Health Technology Assessment (HTA); Head, Department of Health Technology & Services Research, University of Twente, Enschede, The Netherlands; [11]Vice President and Chief Performance Improvement Officer, Illinois Divisions and HSHS Medical Group, Hospital Sisters Health System (HSHS), Belleville, IL. USA; [12]Associate Professor - Healthcare Policy & Research, Lead, Information and Decision Engineering, Mayo Clinic Kern Center for the Science of Health Care Delivery, Rochester, MN, USA

Forum Objectives

- Planning or managing health services involves tough questions
  - What's the cheapest way to protect my population against infection?
  - the best time to start pharmacotherapy for patients with a degenerative condition?
  - How do I ensure that my cancer patient gets the lowest radiation dose possible?
  - That scarce organs go to those who need them most?
  - How do you select and manage the portfolio for health technology development?

Forum Objectives

- Gut feel and simple rules of thumb aren't enough
- The ISPOR Optimization Task Force has reviewed current practice on the use of cutting-edge mathematical techniques
  - Task Force – Report 1
  - Task Force – (Upcoming) Report 2
  - Short Course
- Our Forum will cover:
  - Optimization checklist - Jon
  - Applications (mix of prevention strategies for cervical cancer, timing of statin treatment) – Nasuh
  - Skill development - Praveen

Jon Tosh, DRG Abacus

OPTIMIZATION METHODS AND THE TASK FORCE CHECKLIST

Optimization

- A set of methods to find the best from a set of potential solutions
  - Respect constraints (budget, resources)
  - Many possible potential solutions
  - Methods are designed to be systematic and efficient
- Used in a range of fields (logistics, manufacturing, military)
  - A range of established and emergent uses in health systems
- Framing your problem as an ‘optimization problem’ is crucial, to enable an optimization method to solve it

Healthcare Optimization

	Surgical problem	Health Care	Terminology
Options available	Old or new device	pharma, bundled episodic payment models, ortho, hip/knee, etc	Decision variables
Constraints	Total cost < $150	Budget constraint	Constraints
Aim	Maximize number of QALYs	Maximize health care benefits	Objective function
Evidence base	Cost of each device, how many QALYs are generated and procedure time	Costs of each intervention, health benefits, and any other relevant data	Model (to determine the objective function and Constraints)
Complexity	One-off, deterministic, static problem	Repeated, stochastic, dynamic problem	Optimization method

Complexity

Complexity	Surgery problem	Health Care
Static vs Dynamic	Static (i.e. one-off) problem. If the health center problem was solved for multiple time periods, then it will become dynamic problem	Dynamic problem. Health care is constantly evolving – changing budgets, new policies, new interventions, etc
Deterministic vs stochastic	All the information is assumed to be certain (e.g. costs of the procedure, QALYs, procedure time	Know that the information is uncertain (i.e. uncertainty in the costs and benefits of the interventions)
Linear vs Non-linear	Linear (i.e. each procedure costs the same and achieves the same amount of QALYs)	Non-linear (e.g. Quality/outcomes maybe non-linear, also interactions between the interventions, etc)

Task Force – Optimization Checklist

- ISPOR Optimization Good Practice Guidelines Checklist
- Full Checklist will be published in report 2
- Developed with multiple objectives:
  - A guide for understanding optimization methods
  - A guide for undertaking and reporting optimization
  - A process for reviewing and critiquing the appropriateness and robustness of an optimization application
- We hope the Checklist is optimal in meeting these objectives

Optimization Checklist (1/2)

Steps	Description
Problem structuring	a. Develop a clear description of the decision problem (i.e. objective and constraints, decision variables and parameters) b. Validation and report the decision problem
Mathematical formulation	a. Report and justify the objective function and constraint formulations b. Report and justify the decision variables and parameters
Model development	a. Report and justify the model structure and assumptions b. Report and justify the model representing the objective function and constraints
Model validation	a. Justify and validate the model is appropriate for evaluating all possible scenarios (i.e. different combinations of decision variables and parameters) b. Report the results of model validation

Optimization Checklist (2/2)

Steps	Description
Selection optimization method	a. Report and justify the optimization method chosen b. Report and justify the optimization algorithm chosen
Perform optimization/ sensitivity analysis	a. Report the optimal solution and validate the performance of the optimal soluation b. Report and validate the optimal solution for sensitivity analysis
Report results	a. Report the results of optimal solution and sensitivity analyses b. Examine the optimal solution and sensitivity analyses
Decision making	a. Interpret the optimal solution and sensitivity analysis results b. Report how the optimal solution is used for decision making

Task Force – Optimization Checklist

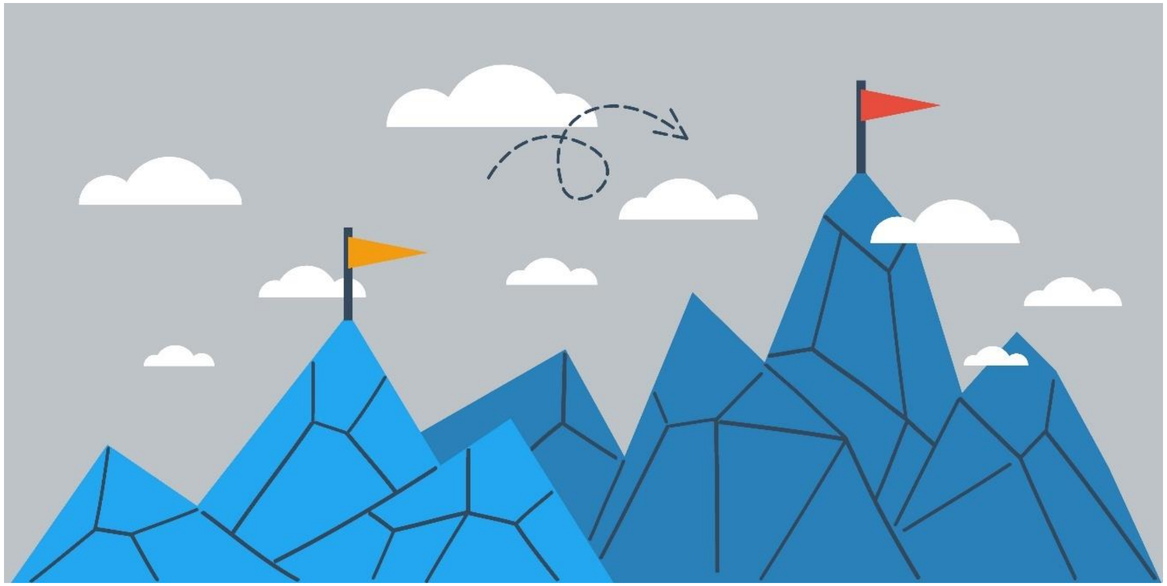
- The Checklist is not intended to prescribe the choice of specific optimization methods
  - Problems are often unique, and therefore methods are problem-contingent
- Checklist covers the key considerations when designing, reporting and assessing an optimization problem
- Aims to be consistent with general recommendations for the designing, reporting and assessment of any quantitative/modelling study

Nasuh Buyukkaramikli,
iMTA & ESHPM

APPLICATION OF OPTIMIZATION METHODS

In the HTA community:

- Optimization is already being used as an analysis tool
  - e.g. calibration of HE models, MCDA, other
- Potential as a decision supporting tool?
  - Guidelines & aligning HTA with healthcare service delivery



Current economic evaluations

- Mostly to help decision makers to include (or not) a new technology in the reimbursement list
  - Price negotiations / managed entry agreements
- Based on clinical needs, clinical and cost-effectiveness evidence and budget-impact
  - How about constraints other than budget? (e.g. human resource or geographical equity constraints)
  - What happens after the reimbursement decision?

Optimization applications (as a decision support tool)

- Case study 1: Optimal mix of prevention strategies against cervical cancer (Demartaeu et al. 2012)
- Case study 2: Optimal statin treatment initiation (Denton et al. 2009)
- Other potential areas in which optimization can support decision making in the current HTA landscape

Optimal mix of prevention strategies against cervical cancer

- Population: women at risk for cervical cancer
- Prevention strategies against cervical cancer in UK and Brazil:
  - Only cytology-based screening (Every year, every 2 years, … , every 25 years
  - Only HPV vaccination
  - Screening plus vaccination (Every year, every 2 years, … , every 25 years)
  - No prevention
- Aim: to minimize the number of cervical cancer cases by mix of strategies
- Under total population, budget, screening and vaccination coverage constraints

Optimal mix of prevention strategies against cervical cancer

- HE Markov model to estimate the outcome of each prevention strategy & linear programming (LP) optimization to identify the optimal prevention strategy mix in the UK and in Brazil
  - Mix of vaccination plus screening and vaccination alone
- 41% and 54% reduction of cervical cancer in the UK and in Brazil with the same budget (prevention and treatment)
- Additional considerations (to be explored in future research)
  - e.g. transmission to the others, decreased secondary infections, infertility avoidance, logistic, socio-economic and equity concerns, etc.)

- **optimization methods informed:**

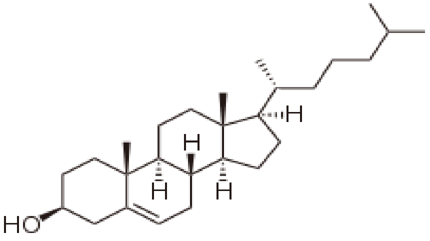
not only whether the HPV vaccination should be reimbursed or not, but also how it should be incorporated to the other prevention strategies to get the best outcomes.

Optimizing statin treatment management using MDP

- Population: T2D patients at risk of complications
- Decision: at each epoch (2 year intervals), start, stop or switch a type of statin treatment
- 324 health states describing various combinations of cholesterol and HDL levels, stroke and CHD states.
- Transition probabilities based on the treatment received and known risk equations
  - (e.g. Framingham, UKPDS or Archimedes)
- Aim: to maximise the discounted net monetary benefit

$$E(NMB) = \Delta QALYs * \lambda - \Delta Cost$$

'One large pepperoni with extra statin'



optimizing statin treatment management using MDP

- MDP formulation (stochastic, dynamic)
- Optimal statin treatment algorithm found
  - different patient characteristics
  - different risk equations
  - different WTP
- Earlier or later statin initiation based on patient characteristics
  - personalised treatment plan
- Additional considerations (future research)
  - resource capacity constraints, drug interactions etc.

- **optimization informed:**

not only whether a type of statin treatment should be reimbursed or not, but how to manage the statin treatment to get the best outcomes for a given patient. (similar applications in cancer screening/ HIV treatment management)

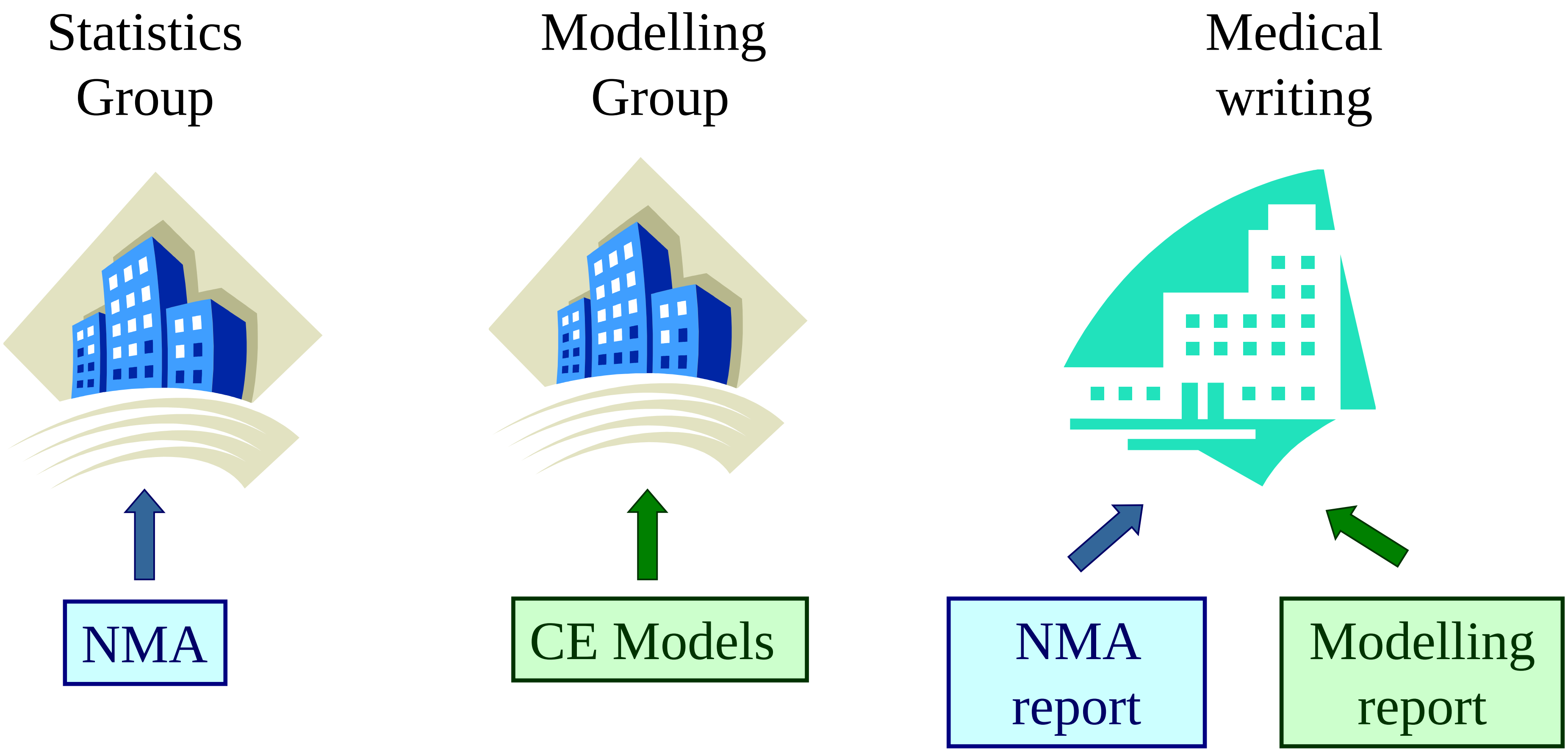
Optimization as decision support tool?

- When combining different prevention/treatment strategies is possible
  - Too many number of treatment alternatives to compare with each other in a classical economic evaluation (case 1)
- Personalized medicine
  - Reimbursement might be based on an average cohort, but treatment decision based on individual characteristics (case 2)
- HTA under different constraints/ additional interactions
  - Capacity constraints
    - Human/infrastructure capacities in developing nations
    - Hep-C: investment capacity due to new oral DAAs. (NHS England may prioritise Hep-C treatment with new DAAs based on highest unmet clinical need, FAD from TA413)
  - HE implications of using two interventions simultaneously are not incremental
- R&D portfolio and pricing strategies of the manufacturer

Praveen Thokala
University of Sheffield

DEVELOPING SKILLS IN OPTIMIZATION

A sample problem: HE company



Project requirements

- Technical input
  - NMA project requires:
    - 1 day of **Statistician** time
    - 3 days of **Medical Writing** time
  - Cost effectiveness project requires:
    - 2 days of **Modeller** time
    - 2 days of **Medical Writing** time
  - Profit from each project:
    - £3,000 from NMA project
    - £5,000 from modelling project

Project requirements

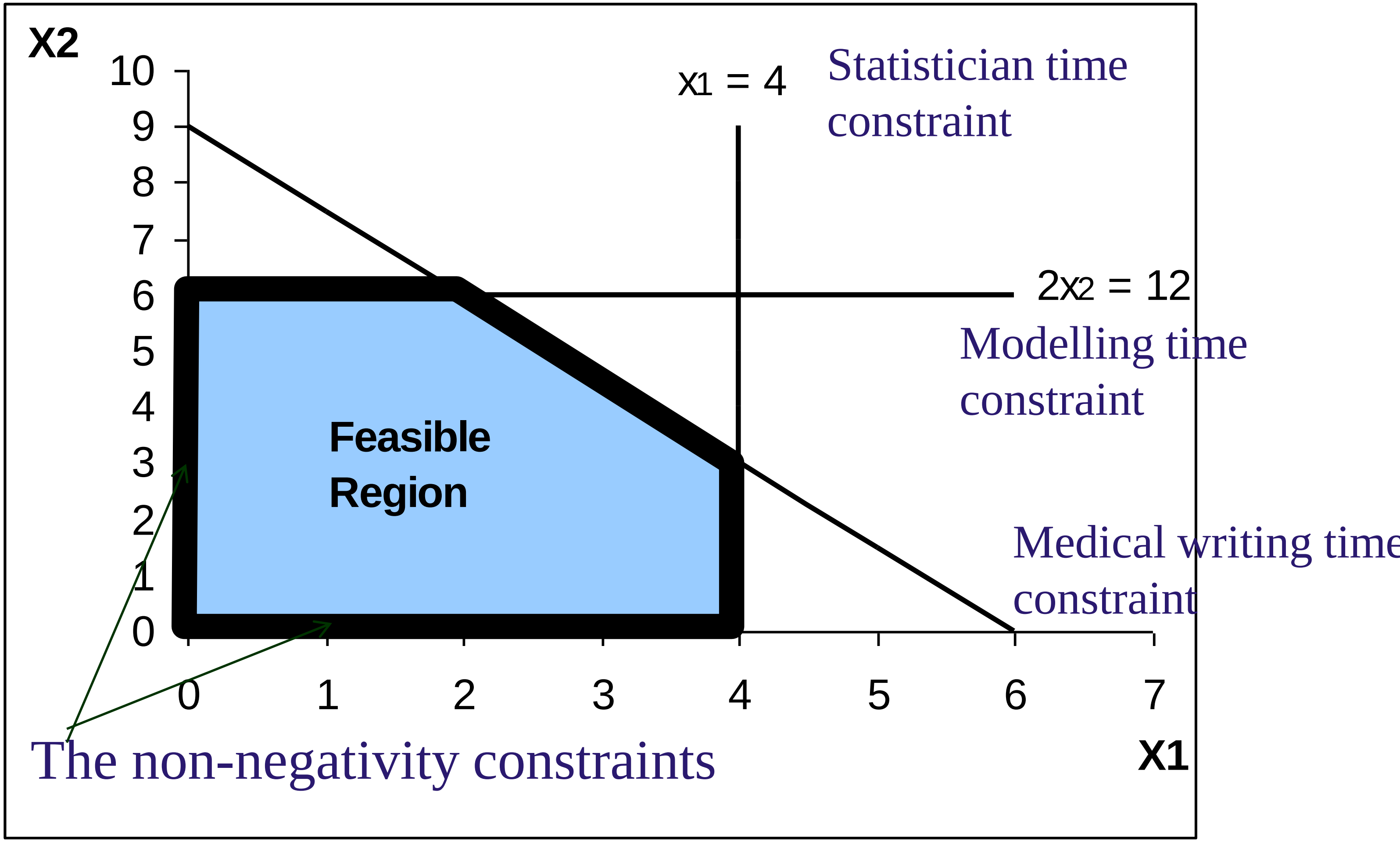
- Capacity each month is limited
  - 4 days of **Statistician** time
  - Twelve days of **Modeller** time
  - Eighteen days of **Medical writing** time

Linear programming formulation

$$\textit{Maximise}\ F = 3x_1 + 5x_2 \quad \text{(profit)}$$

$$
\begin{aligned}
x_1 & & &\leq 4 && \text{(Statistician time constraint)}\\
& & 2x_2 &\leq 12 && \text{(Modeller time constraint)}\\
3x_1 &+ & 2x_2 &\leq 18 && \text{(Medical writing time)}\\
x_1 & & &\geq 0 && \text{(Non-negativity)}\\
& & x_2 &\geq 0 && \text{(Non-negativity)}
\end{aligned}
$$

Graphical solution



Project requirements

- A *linear programming problem* is the problem of maximizing (or minimizing) a linear function subject to a finite number of linear constraints.
- Standard form:

$$\text{maximize} \quad \sum_{j=1}^{n} c_j x_j$$

$$\text{subject to} \quad \sum_{j=1}^{n} a_{ij} x_j \leq b_i \quad (i = 1, 2, \ldots, m)$$

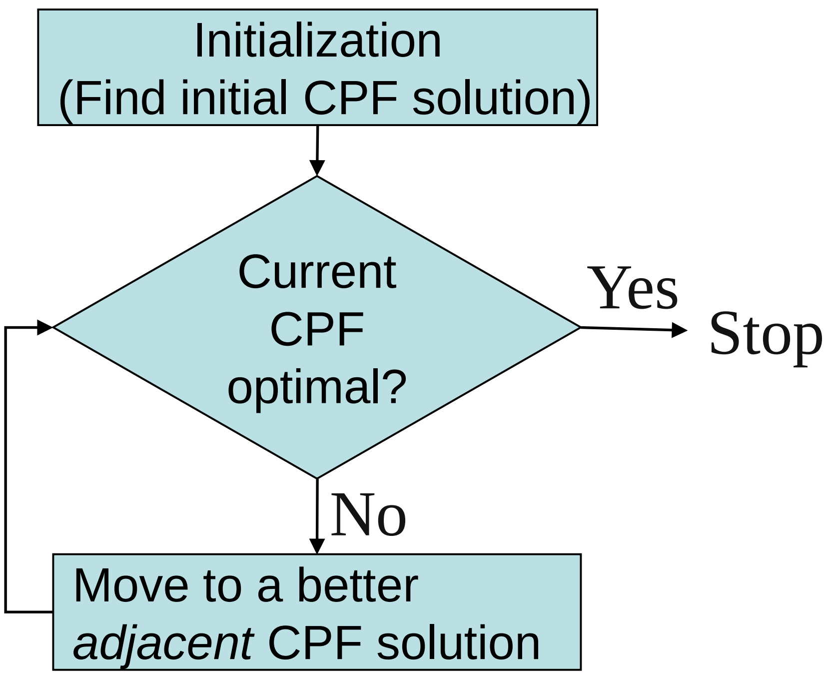
$$x_j \geq 0 \quad (j = 1, 2, \ldots, n)$$

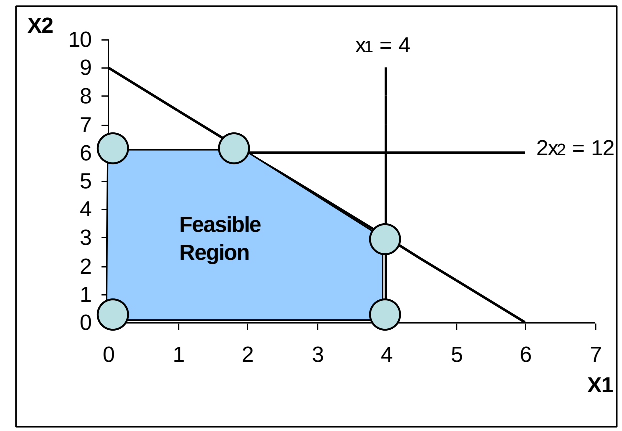
LP Assumptions

1. Proportionality
2. Additivity → Linearity
3. Divisibility
4. Certainty

Simplex method

An *iterative* procedure





- Initial CPF
- Optimality test
- If not optimal, then move to a better adjacent CPF solution:
  - Move along the edges, stop at the first constraint boundary
  - Solve for the intersection of the new boundaries
  - Back to optimality test

Specify LP in Excel

Variables

Constraints

Objective function

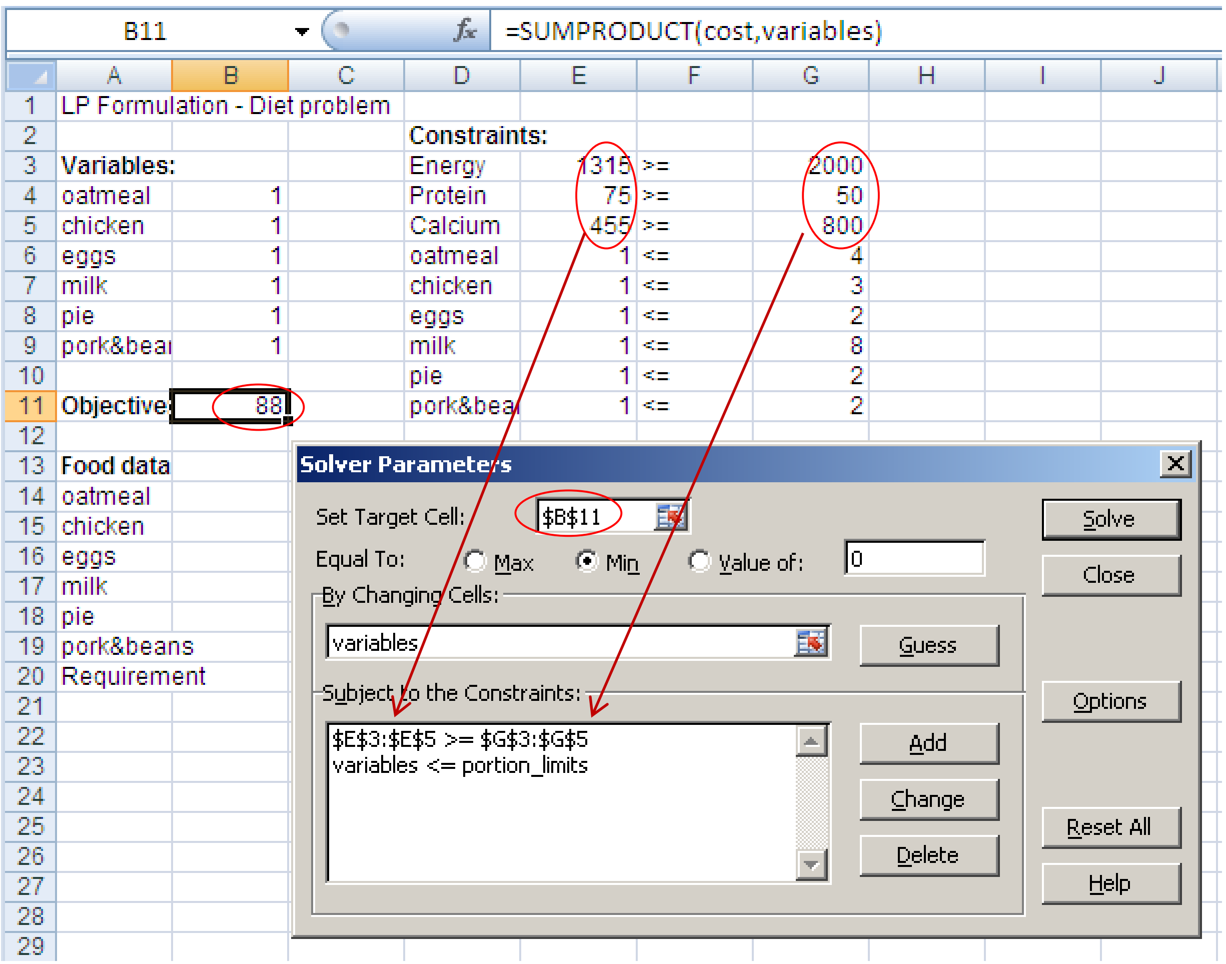
Constant parameters

E11 | f_x | =B9

	A	B	C	D	E	F	G
1	LP Formulation - Diet problem						
2				**Constraints:**			
3	**Variables:**			Energy	1315	>=	2000
4	oatmeal	1		Protein	75	>=	50
5	chicken	1		Calcium	455	>=	800
6	eggs	1		oatmeal	1	<=	4
7	milk	1		chicken	1	<=	3
8	pie	1		eggs	1	<=	2
9	pork&bea	1		milk	1	<=	8
10				pie	1	<=	2
11	**Objective:**	88		pork&bea	1	<=	2
12							
13	**Food data**		Cost	Energy	Protein	Calcium	Limit
14	oatmeal		3	110	4	2	4
15	chicken		24	205	32	12	3
16	eggs		13	160	13	54	2
17	milk		9	160	8	285	8
18	pie		20	420	4	22	2
19	pork&beans		19	260	14	80	2
20	Requirement			2000	50	800	

Using MS Excel Solver

- Name the constraints and objective function



Constraints can be either cell ranges or named ranges, but they have to be of the same size

Also, they should have same type of ‘inequality’ e.g. either all “<=“ or “>=“ but not a mix

Excel Solver output

- The output report contains the objective function, adjustable cells and constraints

Microsoft Excel 12.0 Answer Report

Microsoft Excel 12.0 Answer Report
Worksheet: [LP Diet Problem.xlsx]LP Diet
Report Created: 25/02/2014 09:31:04

Target Cell (Min)

Cell	Name	Original Value	Final Value
$B$11	Objective:	88	92.5

Adjustable Cells

Cell	Name	Original Value	Final Value
$B$4	oatmeal	1	4
$B$5	chicken	1	0
$B$6	eggs	1	0
$B$7	milk	1	4.5
$B$8	pie	1	2
$B$9	pork&beans	1	0

Constraints

Cell	Name	Cell Value	Formula	Status	Slack
$E$3	Energy	2000	$E$3>=$G$3	Binding	0
$E$4	Protein	60	$E$4>=$G$4	Not Binding	10
$E$5	Calcium	1334.5	$E$5>=$G$5	Not Binding	534.5
$B$4	oatmeal	4	$B$4<=$G$14	Binding	0
$B$5	chicken	0	$B$5<=$G$15	Not Binding	3
$B$6	eggs	0	$B$6<=$G$16	Not Binding	2
$B$7	milk	4.5	$B$7<=$G$17	Not Binding	3.5
$B$8	pie	2	$B$8<=$G$18	Binding	0
$B$9	pork&beans	0	$B$9<=$G$19	Not Binding	2

The initial values and final (optimal) values of the target cell (objective function) and the adjustable cells (decision variables) are presented.

Binding constraints imply that the LHS and RHS are equal at the optimal values of decision variables. Not binding implies they are not equal, the difference is presented as ‘slack’

Optimization Task Force
Forum Presenters

DISCUSSION