CS481: Bioinformatics Algorithms

Can Alkan
EA509
calkan@cs.bilkent.edu.tr

http://www.cs.bilkent.edu.tr/~calkan/teaching/cs481/

CS481

- Class hours:
  - Online-only weeks:
    - Tue 9:00-10:00 - Thu 15:30-17:20
  - Hybrid weeks:
    - Tue 9:30-10:20 (in class) - Thu 17:30-19:20 (online)
- Class room: EB104 / Zoom
- Office hour: Wed 14:00-15:00
  - meet.google.com/nhm-ieor-qke
- TA: Ricardo Román Brenes: ricardo@bilkent.edu.tr
- Grading:
  - 1 midterm: 25%
  - 1 final: 35%
  - Homeworks (programming): 40% (n=7-8)

CS481

- Recommended Textbooks
  - Genome Scale Algorithm Design, Veli Makinen, et al., Cambridge University Press, 2015
  - An Introduction to Bioinformatics Algorithms (Computational Molecular Biology), Neil Jones and Pavel Pevzner, MIT Press, 2004
  - https://www.bioinformaticsalgorithms.org/
- Additional:
  - Algorithms on Strings, Trees, and Sequences: Computer Science and Computational Biology, Dan Gusfield, Cambridge University Press
  - Biological Sequence Analysis: Probabilistic Models of Proteins and Nucleic Acids, Richard Durbin, Sean R. Eddy, Anders Krogh, Graeme Mitchison, Cambridge University Press
  - Bioinformatics: The Machine Learning Approach, Second Edition, Pierre Baldi, Soren Brunak, MIT Press
  - ROSALIND problem sets: http://rosalind.info/problems/locations/

CS481

- This course is about **algorithms** in the field of bioinformatics:
  - What are the problems?
  - What algorithms are developed for what problem?
  - Algorithm design techniques
- This course is **not** about how to analyze biological data using available tools:
  - Recommended course: MBG 326: Introduction to Bioinformatics

CS481 and other courses

- Includes elements from:
  - CS201/202: data structures -- implicit prerequisite
  - CS473: algorithms, dynamic programming, greedy algorithms, branch-and-bound, etc.
  - CS476: complexity, context-free grammars, DFA/NFA
  - CS464: hidden Markov models (not covered in CS481, but related topic)

CS481: Assumptions

- You are assumed to know/understand
  - Computer science basics (CS101/102 or CS111/112)
    - CS201/202 would be better
    - CS473 would be even better
  - Data structures (trees, linked lists, queues, etc.)
  - Elementary algorithms (sorting, hashing, etc.)
  - Programming: C, C++ (preferred); Python, Java
    - Note: we will give bonus points for the “fastest” code in some homeworks
- You don’t *have to* be a “biology expert” and **we will not teach any biology** in this course: MBG 110 would be sufficient

Bioinformatics Algorithms

- Development of methods based on computer science for problems in biology and medicine
  - Sequence analysis (combinatorial and statistical/probabilistic methods)
  - Graph theory
  - Data mining
  - Database
  - Statistics
  - Image processing
  - Visualization
  - …..

CS 481

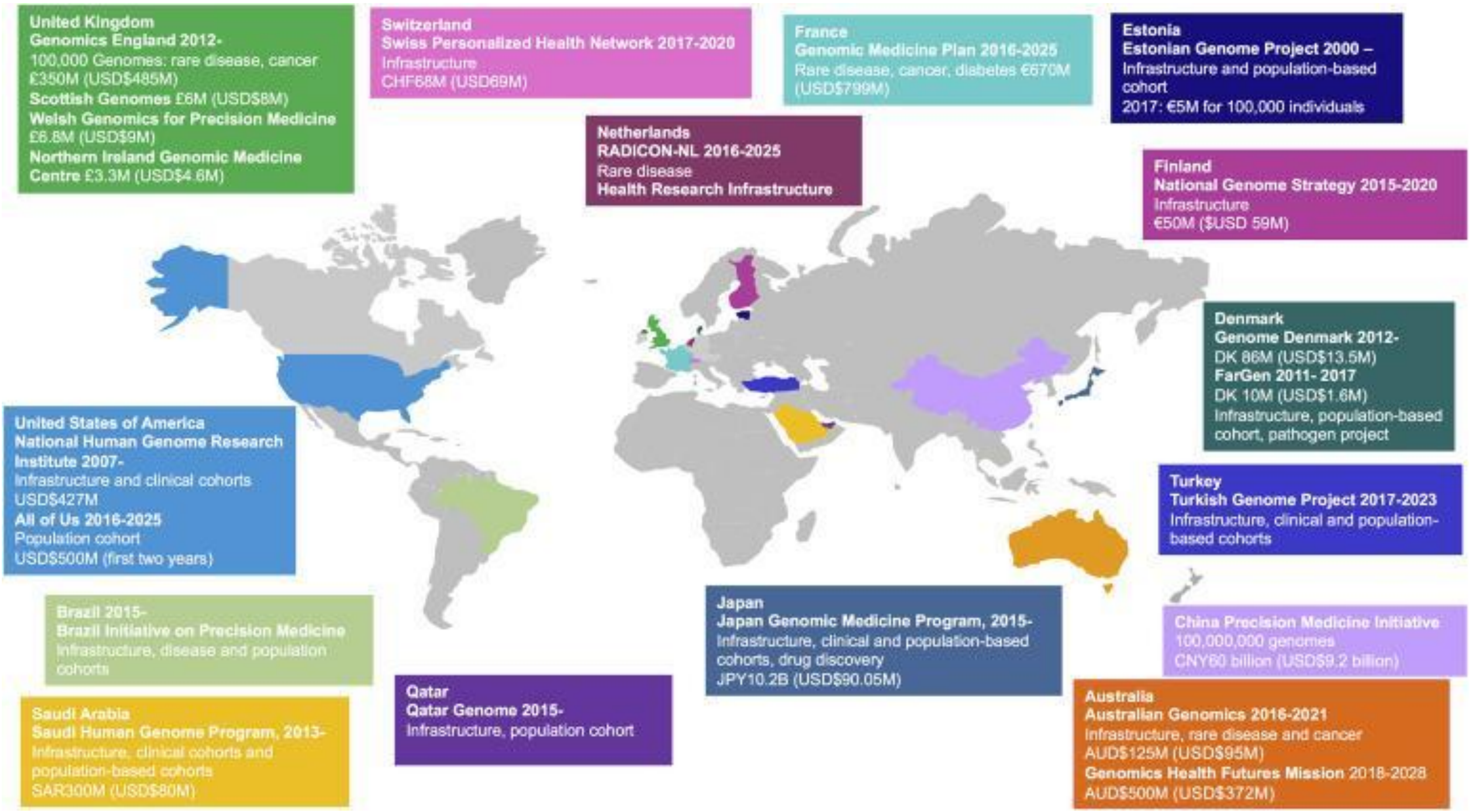
Bioinformatics: Applications

- Human disease
    - Personalized Medicine
- Genomics: Genome analysis, gene discovery, regulatory elements, etc.
- Population genomics
- Evolutionary biology
- Proteomics: analysis of proteins, protein pathways, interactions
- Transcriptomics: analysis of the transcriptome (RNA sequences)
- …

Why would you learn these algorithms?

- Most developed for research within other fields that include string processing, clustering, text-pattern search, etc.
- Bioinformatics (non-academic) jobs on the rise:
  - Genomics England, Genome Asia, etc.: 100,000 genome projects
  - DNAnexus, SevenBridges, LifeBit: genome analysis on the cloud.

Genomics and healthcare



United Kingdom
Genomics England 2012-
100,000 Genomes: rare disease, cancer
£350M (USD$485M)
Scottish Genomes £6M (USD$8M)
Welsh Genomics for Precision Medicine
£6.8M (USD$9M)
Northern Ireland Genomic Medicine Centre £3.3M (USD$4.6M)

Switzerland
Swiss Personalized Health Network 2017-2020
Infrastructure
CHF68M (USD69M)

France
Genomic Medicine Plan 2016-2025
Rare disease, cancer, diabetes €670M
(USD$799M)

Estonia
Estonian Genome Project 2000 –
Infrastructure and population-based cohort
2017: €5M for 100,000 individuals

Netherlands
RADICON-NL 2016-2025
Rare disease
Health Research Infrastructure

Finland
National Genome Strategy 2015-2020
Infrastructure
€50M ($USD 59M)

Denmark
Genome Denmark 2012-
DK 86M (USD$13.5M)
FarGen 2011- 2017
DK 10M (USD$1.6M)
Infrastructure, population-based cohort, pathogen project

United States of America
National Human Genome Research Institute 2007-
Infrastructure and clinical cohorts
USD$427M
All of Us 2016-2025
Population cohort
USD$500M (first two years)

Turkey
Turkish Genome Project 2017-2023
Infrastructure, clinical and population-based cohorts

Brazil 2015-
Brazil Initiative on Precision Medicine
Infrastructure, disease and population cohorts

Japan
Japan Genomic Medicine Program, 2015-
Infrastructure, clinical and population-based cohorts, drug discovery
JPY10.2B (USD$90.05M)

China Precision Medicine Initiative
100,000,000 genomes
CNY60 billion (USD$9.2 billion)

Qatar
Qatar Genome 2015-
Infrastructure, population cohort

Saudi Arabia
Saudi Human Genome Program, 2013-
Infrastructure, clinical cohorts and population-based cohorts
SAR300M (USD$80M)

Australia
Australian Genomics 2016-2021
Infrastructure, rare disease and cancer
AUD$125M (USD$95M)
Genomics Health Futures Mission 2018-2028
AUD$500M (USD$372M)

Stark et al., AJHG 2019

(VERY) BRIEF INTRODUCTION TO COMPLEXITY

Tractable vs intractable

- Tractable problems: there exists a solution with O(f(n)) run time, where f(n) is *polynomial*
- *P* is the set of problems that are **known** to be *solvable* in polynomial time
- *NP* is the set of problems that are *verifiable* in polynomial time (or, solvable by a non-deterministic Turing Machine in polynomial time)
  - *NP: "non-deterministically polynomial"*

$$P \subset NP$$

NP-hard

- *NP-hard:* non-deterministically polynomial - hard
  - Set of problems that are "*at least as hard as the hardest problems in NP*"
  - There are no known polynomial time optimal solutions
  - There *may* be polynomial-time *approximate* solutions

NP-Complete

- A *decision problem* C is in NPC if :
  - C is in NP
  - Every problem in NP is **reducible** to C in polynomial time

That means: if you could solve any NPC problem in polynomial time, then you can solve all of them in polynomial time

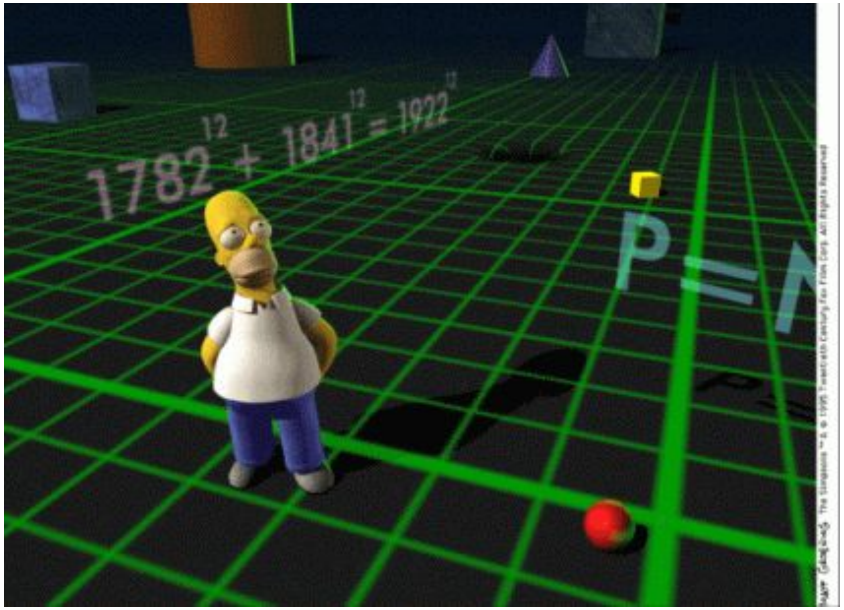
Decision problems: outputs “yes” or “no”

NP-intermediate

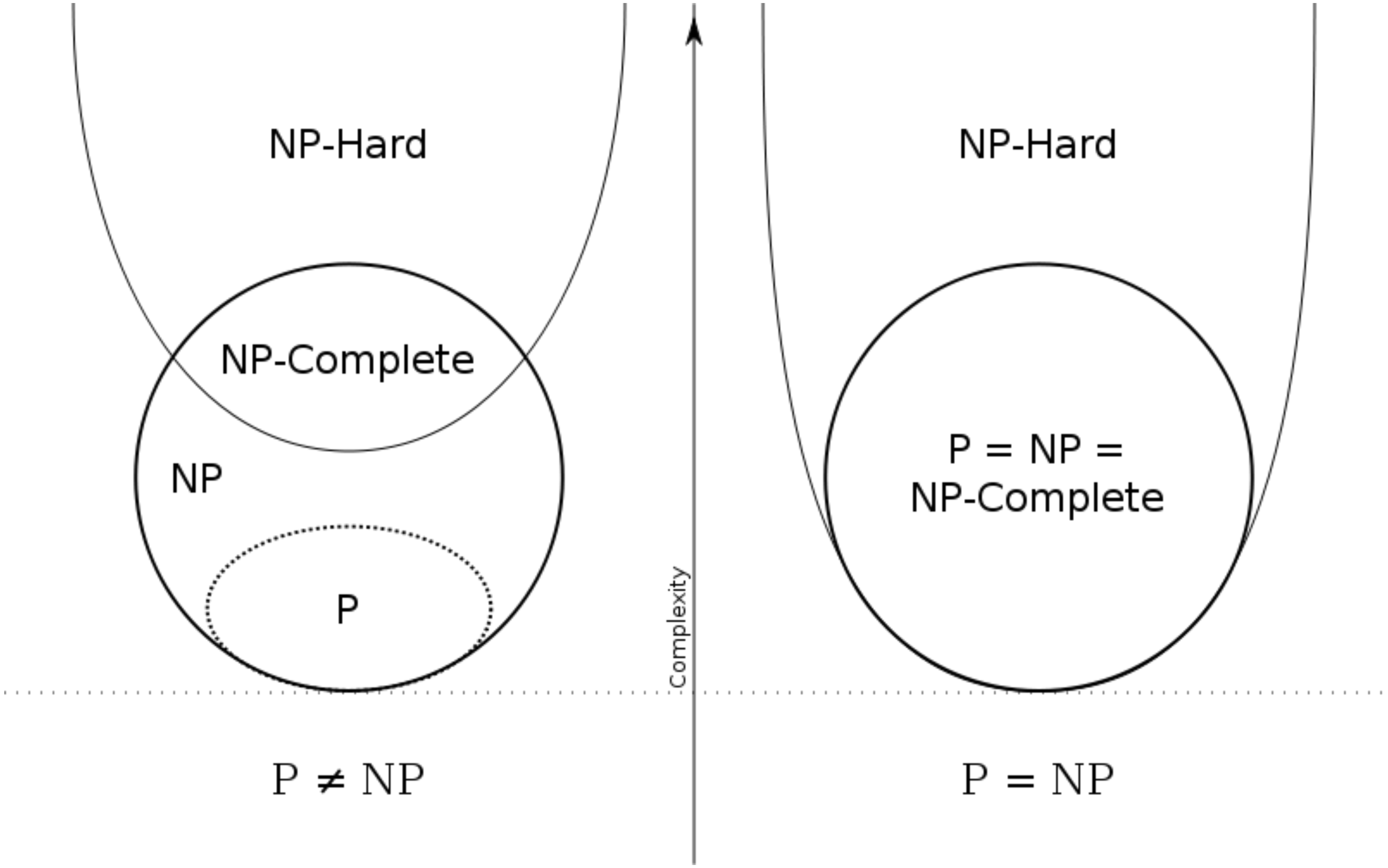
- Problems that are in NP; but not in either NPC or NP-hard (as far as we know)

P vs. NP

- We do not know whether P=NP or P≠NP
    - Principal unsolved problem in computer science
    - Most likely P≠NP



P vs. NP vs. NPC vs. NP-hard



Examples

- P:
  - Sorting numbers, searching numbers, pairwise sequence alignment, etc.
- NP-complete:
  - Subset-sum, traveling salesman, etc.
- NP-intermediate:
  - Factorization, graph isomorphism, etc.

Historical reference

- The notion of NP-Completeness: Stephen Cook and Leonid Levin independently in 1971
  - First NP-Complete problem to be identified: Boolean satisfiability problem (SAT)
    - Cook-Levin theorem
- More NPC problems: Richard Karp, 1972
  - “21 NPC Problems”
- Now there are thousands….

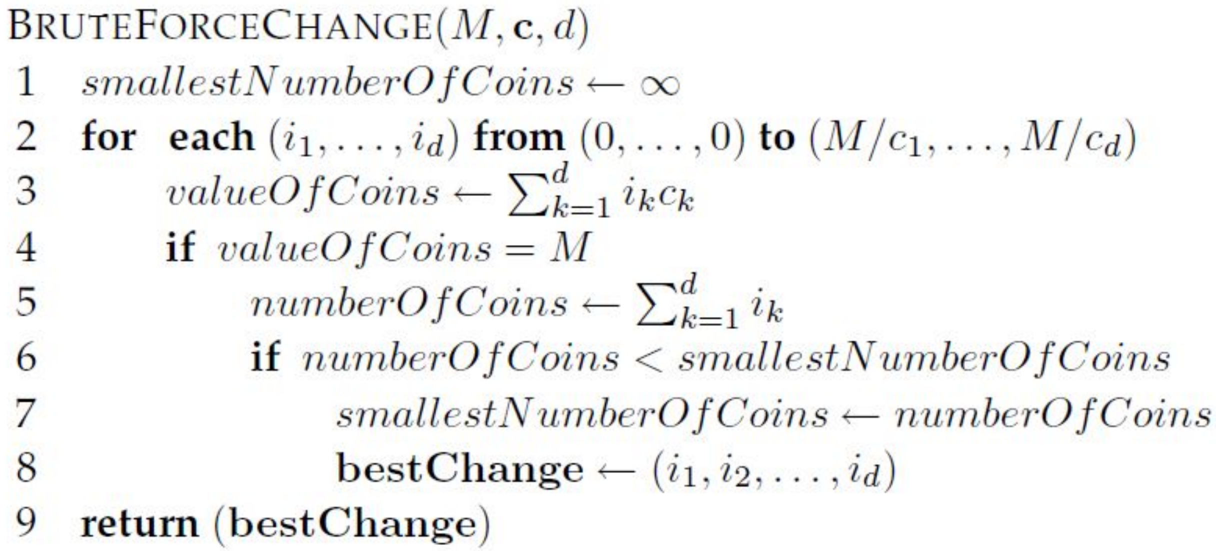
ALGORITHM DESIGN TECHNIQUES

Sample problem: Change

- Input: An amount of money M, in cents
- Output: Smallest number of coins that adds up to M
  - Quarters (25c): q
  - Dimes (10c): d
  - Nickels (5c): n
  - Pennies (1c): p
  - Or, in general, c_1, c_2, …, c_d (*d* possible denominations)

Algorithm design techniques

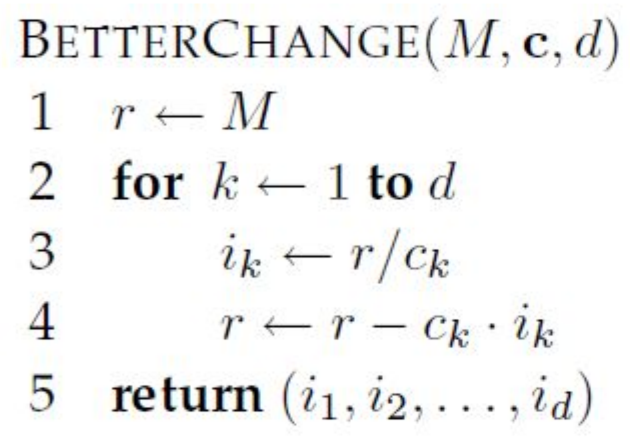
- **Exhaustive search / brute force**
  - Examine every possible alternative to find a solution



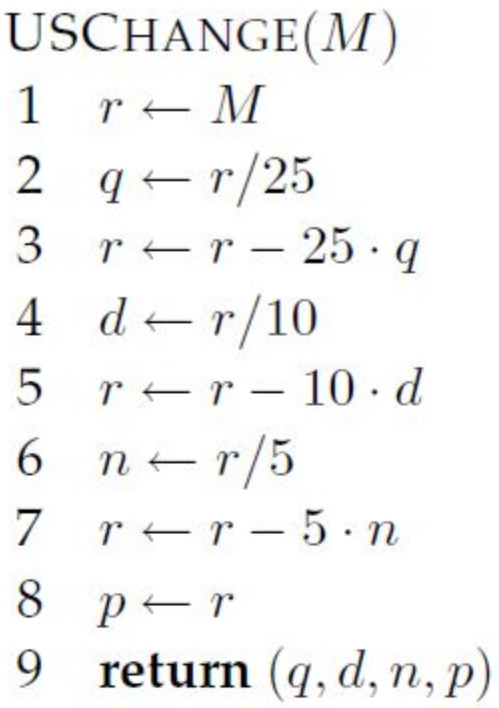
```
BRUTEFORCECHANGE($M, \mathbf{c}, d$)
smallestNumberOfCoins $\leftarrow \infty$
for each $(i_1, \ldots, i_d)$ from $(0, \ldots, 0)$ to $(M/c_1, \ldots, M/c_d)$
    valueOfCoins $\leftarrow \sum_{k=1}^{d} i_k c_k$
    if valueOfCoins $= M$
        numberOfCoins $\leftarrow \sum_{k=1}^{d} i_k$
        if numberOfCoins $<$ smallestNumberOfCoins
            smallestNumberOfCoins $\leftarrow$ numberOfCoins
            bestChange $\leftarrow (i_1, i_2, \ldots, i_d)$
return (bestChange)
```

Algorithm design techniques

- **Greedy algorithms:**
    - Choose the “most attractive” alternative at each iteration



```
BETTERCHANGE($M$, $\mathbf{c}$, $d$)
r ← M
for k ← 1 to d
        $i_k \leftarrow r / c_k$
        $r \leftarrow r - c_k \cdot i_k$
return $(i_1, i_2, \ldots, i_d)$
```



```
USCHANGE($M$)
$r \leftarrow M$
$q \leftarrow r / 25$
$r \leftarrow r - 25 \cdot q$
$d \leftarrow r / 10$
$r \leftarrow r - 10 \cdot d$
$n \leftarrow r / 5$
$r \leftarrow r - 5 \cdot n$
$p \leftarrow r$
return $(q, d, n, p)$
```

Algorithm design techniques

- **Dynamic Programming:**
  - Break problems into subproblems; solve subproblems; merge solutions of subproblems to solve the real problem
  - Keep track of computations to avoid recomputing values that you already solved
    - *Dynamic programming table*

DP example: Rocks game

- Two players
- Two piles of rocks with p_1 rocks in pile 1, and p_2 rocks in pile 2
- In turn, each player picks:
    - One rock from either pile 1 or pile 2; OR
    - One rock from pile 1 and one rock from pile2
- The player that picks the last rock wins

DP algorithm for Player 1

- Problem: $p_1 = p_2 = 10$
- Solve more general problem of $p_1 = n$ and $p_2 = m$
- It’s hard to directly calculate for n=5 and m=6; we need to solve smaller problems

DP algorithm for Player 1

	pile2	0	1	2	3	4	5	6	7	8	9	10
	0		W									
pile1	1	W	W									
	2											
	3											
	4											
	5											
	6											
	7											
	8											
	9											
	10											

Initialize; obvious win for Player 1 for 1,0; 0,1 and 1,1

DP algorithm for Player 1

pile2

		0	1	2	3	4	5	6	7	8	9	10
	0		W	L								
pile1	1	W	W									
	2	L										
	3											
	4											
	5											
	6											
	7											
	8											
	9											
	10											

Player 1 cannot win for 2,0 and 0,2

DP algorithm for Player 1

pile2

		0	1	2	3	4	5	6	7	8	9	10
	0		W	L								
pile1	1	W	W	W								
	2	L	W									
	3											
	4											
	5											
	6											
	7											
	8											
	9											
	10											

Player 1 can win for 2,1 if he picks one from pile2

Player 1 can win for 1,2 if he picks one from pile1

DP algorithm for Player 1

pile2

pile1

Player 1 can win for 2,1 if he picks one from pile2

Player 1 can win for 1,2 if he picks one from pile1

DP algorithm for Player 1

pile2

		0	1	2	3	4	5	6	7	8	9	10
	0		W	L								
pile1	1	W	W	W								
	2	L	W	L								
	3											
	4											
	5											
	6											
	7											
	8											
	9											
	10											

Player 1 cannot win for 2,2

Any move causes his opponent to go to W state

DP “moves”

When you are at position *(i,j)*

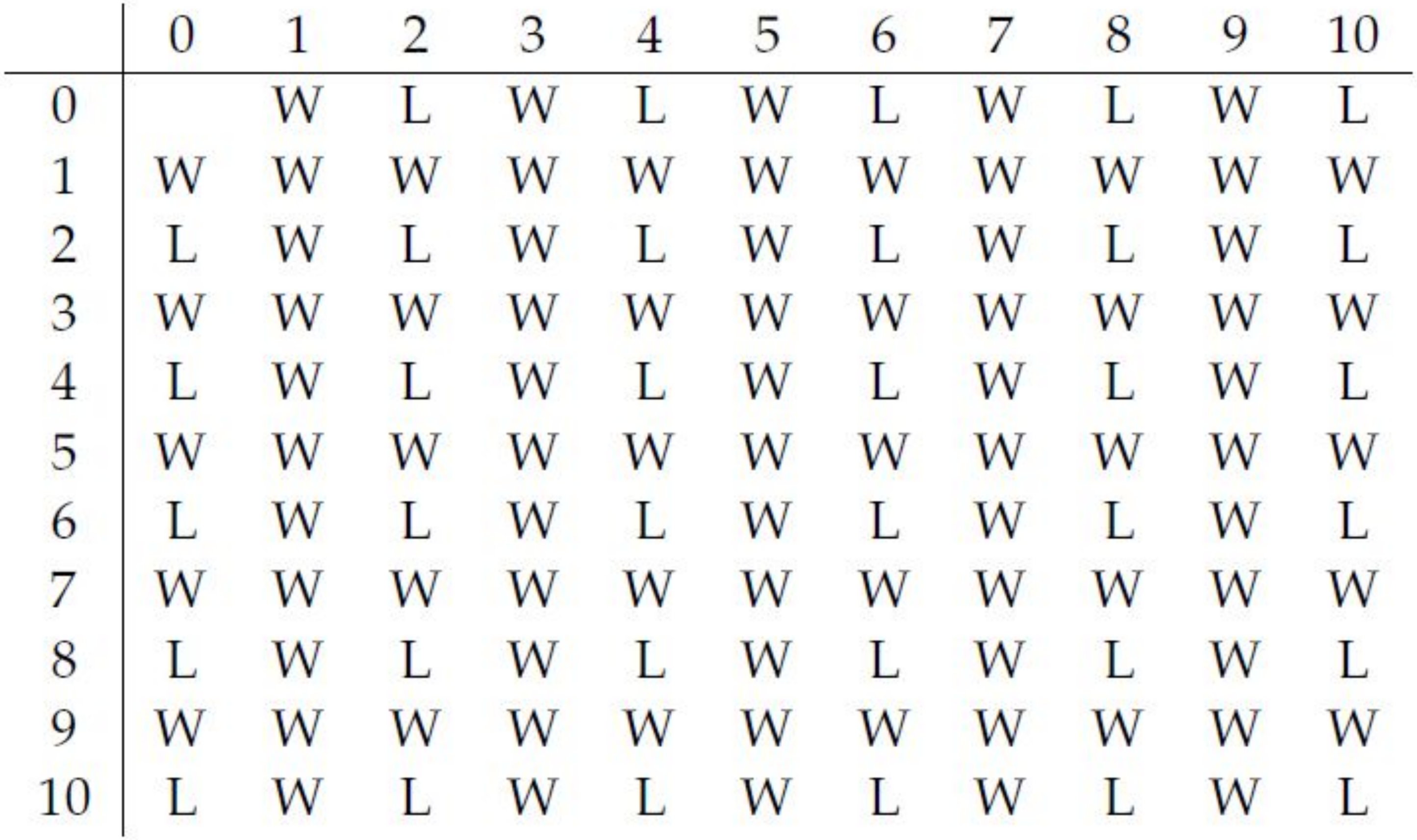
Go to:

Pick from pile 1: ***(i-1, j)***

Pick from pile 2: ***(i, j-1)***

Pick from both piles 1 and 2: ***(i-1, j-1)***

DP final table



	0	1	2	3	4	5	6	7	8	9	10
0		W	L	W	L	W	L	W	L	W	L
1	W	W	W	W	W	W	W	W	W	W	W
2	L	W	L	W	L	W	L	W	L	W	L
3	W	W	W	W	W	W	W	W	W	W	W
4	L	W	L	W	L	W	L	W	L	W	L
5	W	W	W	W	W	W	W	W	W	W	W
6	L	W	L	W	L	W	L	W	L	W	L
7	W	W	W	W	W	W	W	W	W	W	W
8	L	W	L	W	L	W	L	W	L	W	L
9	W	W	W	W	W	W	W	W	W	W	W
10	L	W	L	W	L	W	L	W	L	W	L

Also keep track of the choices you need to make to achieve W and L states: *traceback table*

Algorithm design techniques: CS473

- **Branch and bound:**
  - Omit a large number of alternatives when performing brute force
- **Divide and conquer:**
  - Split, solve, merge
    - Mergesort
- **Machine learning (CS 464):**
  - Analyze previously available solutions, calculate statistics, apply most likely solution
- **Randomized algorithms:**
  - Pick a solution randomly, test if it works. If not, pick another random solution