# Microarray Layout and the Quadratic Assignment Problem

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## Outline

1. Introduction to Microarray Layout
2. Conflict Index Model
3. New Approach: Quadratic Assignment Problem (QAP)

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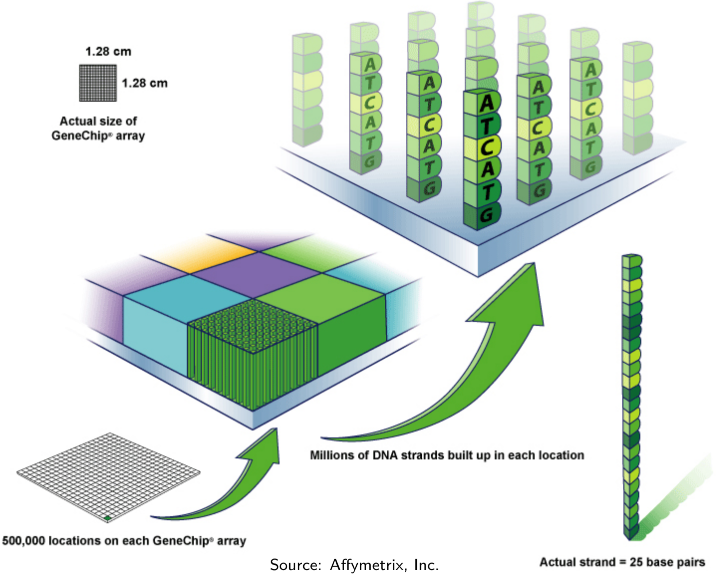
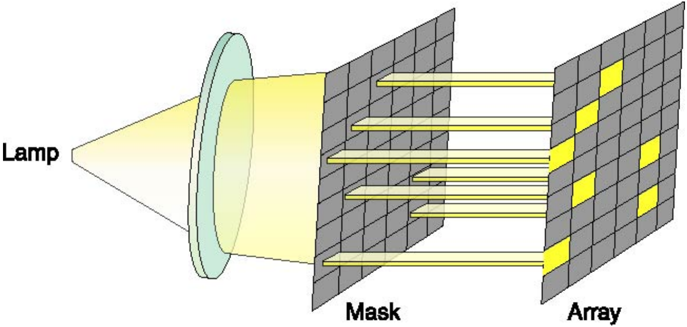
# High-Density Oligonucleotide Microarrays


1.28 cm
1.28 cm
Actual size of GeneChip® array
A T C A T G
500,000 locations on each GeneChip® array
Millions of DNA strands built up in each location
Actual strand = 25 base pairs

Source: Affymetrix, Inc.

# Probe Synthesis with Photolitographic Masks

Source: Affymetrix, Inc.



- Probes are synthesized on the chip in a series of steps
- Each step appends a particular nucleotide to selected regions
- Selection occurs by exposure to light directed by a mask

# Deposition Sequence and Probe Embeddings

| | | |
|---|---|---|
| $p_1$<br>ACT | $p_2$<br>CTG | $p_3$<br>GAT |
| $p_4$<br>TCC | $p_5$<br>GAC | $p_6$<br>GCC |
| $p_7$<br>TAC | $p_8$<br>CGT | $p_9$<br>AAT |

$$S = \text{ACGTACGTACGT}$$
$$\varepsilon_1 = \text{------------}$$
$$\varepsilon_2 = \text{------------}$$
$$\varepsilon_3 = \text{------------}$$
$$\varepsilon_4 = \text{------------}$$
$$\varepsilon_5 = \text{------------}$$
$$\varepsilon_6 = \text{------------}$$
$$\varepsilon_7 = \text{------------}$$
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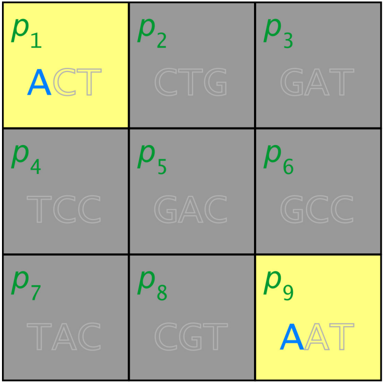
# Deposition Sequence and Probe Embeddings



| | | |
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$S$ = ACGTACGTACGT

$\varepsilon_1$ = A-----------

$\varepsilon_2$ = ------------

$\varepsilon_3$ = ------------

$\varepsilon_4$ = ------------

$\varepsilon_5$ = ------------

$\varepsilon_6$ = ------------

$\varepsilon_7$ = ------------

$\varepsilon_8$ = ------------

$\varepsilon_9$ = A-----------

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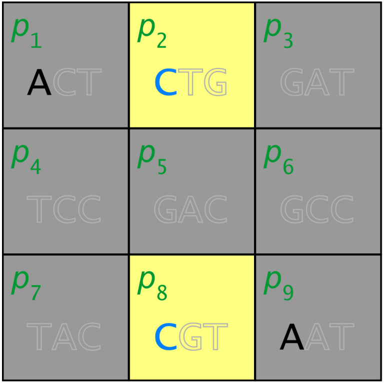

| | | |
|---|---|---|
| $p_1$ ACT | $p_2$ CTG | $p_3$ GAT |
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$S =$ ACGTACGTACGT

$\varepsilon_1 =$ A-----------

$\varepsilon_2 =$ -C----------

$\varepsilon_3 =$ ------------

$\varepsilon_4 =$ ------------

$\varepsilon_5 =$ ------------

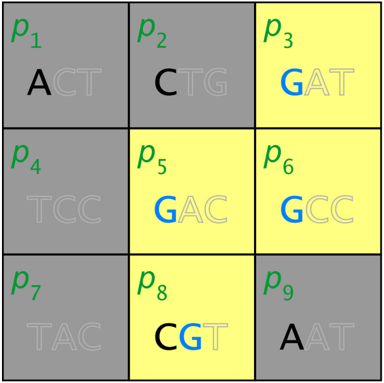
$\varepsilon_6 =$ ------------

$\varepsilon_7 =$ ------------

$\varepsilon_8 =$ -C----------

$\varepsilon_9 =$ A-----------

# Deposition Sequence and Probe Embeddings



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$S$ = ACGTACGTACGT

$\varepsilon_1$ = A-----------

$\varepsilon_2$ = -C----------

$\varepsilon_3$ = --G---------

$\varepsilon_4$ = ------------

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$\varepsilon_7$ = ------------

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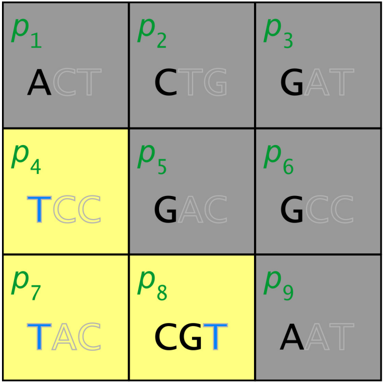
# Deposition Sequence and Probe Embeddings



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$S$ = ACGTACGTACGT

$\varepsilon_1$ = A-----------

$\varepsilon_2$ = -C----------

$\varepsilon_3$ = --G---------

$\varepsilon_4$ = ---T--------

$\varepsilon_5$ = --G---------

$\varepsilon_6$ = --G---------

$\varepsilon_7$ = ---T--------

$\varepsilon_8$ = -CGT--------

$\varepsilon_9$ = A-----------

# Deposition Sequence and Probe Embeddings

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$S =$ ACGTACGTACGT

$\varepsilon_1 =$ A----C-T----

$\varepsilon_2 =$ -C-----T--G-

$\varepsilon_3 =$ --G-A--T----

$\varepsilon_4 =$ ---T-C---C--

$\varepsilon_5 =$ --G-A----C--

$\varepsilon_6 =$ --G--C---C--

$\varepsilon_7 =$ ---TAC------

$\varepsilon_8 =$ -CGT--------

$\varepsilon_9 =$ A---A------T

# Deposition Sequence and Probe Embeddings

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$S$ = ACGTACGTACGT

$\varepsilon_1$ = A----C-T----

$\varepsilon_2$ = -C-----T--G-

$\varepsilon_3$ = --G-A--T----

$\varepsilon_4$ = ---T-C---C--

$\varepsilon_5$ = --G-A----C--

$\varepsilon_6$ = --G--C---C--

$\varepsilon_7$ = ---TAC------

$\varepsilon_8$ = -CGT--------

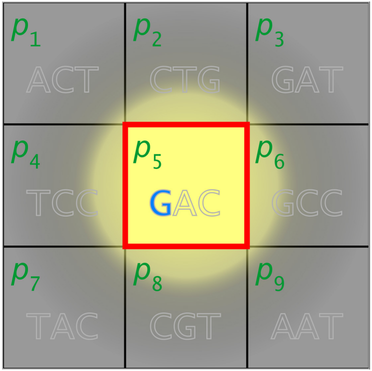
$\varepsilon_9$ = A---A------T

$\varepsilon'_9$ = A-------A--T

Right-most: $\varepsilon''_9$ = ----A---A--T

Left-most: $\varepsilon'''_9$ = A---A--T----

# Unintended Illumination Problem



- Untargeted spots can be accidentally activated
  - Diffraction of light
  - Internal reflection
- Production of defective probes
- More likely near the borders between masked and unmasked spots: border conflict

**Border Length Minimization Problem (Hannenhalli et al., 2002)**

Find arrangement of the probes and embeddings with minimum number of border conflicts over all masks

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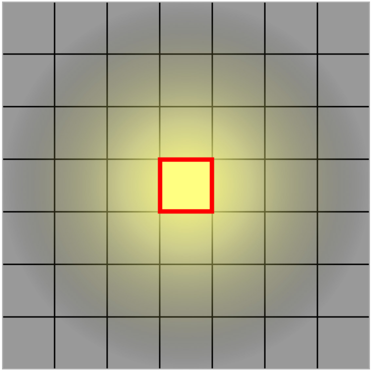
# Motivation

- Border Length measures the quality of a particular mask
    - We are more interested in a per-probe measure
- Practical considerations:
    a) Stray light might damage probes as far as three cells away from the targeted spot
    b) Imperfections in the middle of a probe are more harmful than in its extremities



ATGACTACCATGCAGTACAACATAC

# Definition

## Conflict Index of a probe $p$

$$\mathcal{C}(p) := \sum_{t=1}^{T} \left( \omega(p,t) \sum_{nbs.\,p'} \delta(p,p',t) \right)$$

## Distance-dependent weights

$$\delta(p,p',t) := \begin{cases} (d(p,p'))^{-2} & \text{if } p' \text{ is unmasked at step } t, \\ 0 & \text{otherwise,} \end{cases}$$

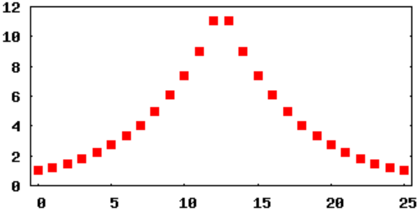
where $d(p,p')$ is the Euclidean distance between the spots of $p$ and $p'$.

| | | | | | | |
|---|---|---|---|---|---|---|
| 0.06 | 0.08 | 0.10 | 0.11 | 0.10 | 0.08 | 0.06 |
| 0.08 | 0.13 | 0.20 | 0.25 | 0.20 | 0.13 | 0.08 |
| 0.10 | 0.20 | 0.50 | 1.00 | 0.50 | 0.20 | 0.10 |
| 0.11 | 0.25 | 1.00 | $p$ | 1.00 | 0.25 | 0.11 |
| 0.10 | 0.20 | 0.50 | 1.00 | 0.50 | 0.20 | 0.10 |
| 0.08 | 0.13 | 0.20 | 0.25 | 0.20 | 0.13 | 0.08 |
| 0.06 | 0.08 | 0.10 | 0.11 | 0.10 | 0.08 | 0.06 |

# Definition

## Conflict Index of a probe $p$

$$\mathcal{C}(p) := \sum_{t=1}^{T}\left(\omega(p,t)\sum_{p'}\delta(p,p',t)\right)$$



## Position-dependent weights

$$\omega(p,t) := \begin{cases} c \cdot \exp\left(\theta \cdot \lambda(p,t)\right) & \text{if } p \text{ is masked at step } t, \\ 0 & \text{otherwise,} \end{cases}$$

where

$$\lambda(p,t) := 1 + \min(b_{p,t}, \ell_p - b_{p,t}),$$

$b_{p,t}$ denotes the number of nucleotides synthesized up to and including step $t$, $\ell_p$ is the length of probe $p$, $c > 0$ and $\theta > 0$ are constants.

# Border Length and Conflict Index

## Redefine $\delta$ and $\omega$ as

$$\delta(p, p', t) := \begin{cases} 1 & \text{if } p' \text{ is a direct neighbor of } p \\ & \text{and is unmasked at step } t, \\ 0 & \text{otherwise} \end{cases}$$

$$\omega(p, t) := \begin{cases} 1/2 & \text{if } p \text{ is masked at step } t, \\ 0 & \text{otherwise} \end{cases}$$

- Then $\sum_p \mathcal{C}(p) = \sum_{t=1}^{T} \mathcal{B}_t$
- Border length and conflict indices are equivalent for this choice of $\delta$ and $\omega$
- For our choices, they are not equivalent but still correlated: a good layout has low border lengths and conflict indices

# New Problem

### Conflict Index Minimization Problem

Find placement of the probes and embeddings such that

$$\sum_p \mathcal{C}(p) \rightarrow \min$$

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# Previous Work: Place and Re-embed

The problem has been traditionally approached in two phases:

1) Placement of probes given a fixed embedding
2) Re-embedding of probes once a placement is fixed

## Placement: Row-epitaxial (Kahng *et al.*, 2003)

- Spots are filled in a pre-defined order
  - Select probe from a list $Q$ such that conflicts with filled spots are minimized
- Restrict the maximum size of $Q$ (e.g. $Q = 20\,000$)

## Re-embedding: several algorithms (Kahng *et al.*, 2002, 2003)

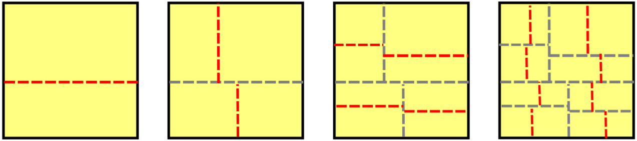
- Based on the Optimum Single Probe Embedding (OSPE)
  - Re-embed a probe optimally in regards to its neighbors
  - Dynamic programming, like a sequence alignment

# Previous Work: Partitioning

- The placement problem can be partitioned
  - Divide the chip into sub-regions; assign sub-sets of probes to each sub-region
  - Sub-regions are processed independently, and can be recursively partitioned
  - A placement algorithm is called on each final sub-region

## Pivot Partitioning (Carvalho & Rahmann, 2006)

- Alternate horizontal and vertical partitions
- Allow sub-regions to have different sizes



# Quadratic Assignment Problem

## Definition

- Given $n \times n$ real-valued matrices $F = (f_{ij}) \geq 0$ and $D = (d_{kl}) \geq 0$
- Find a permutation $\pi$ of $\{1, 2, \ldots n\}$ such that

$$\sum_{i=1}^{n} \sum_{j=1}^{n} f_{ij} \cdot d_{\pi(i)\pi(j)} \longrightarrow \min$$

## Example: Facility Location Problem

- Assign $n$ facilities to $n$ locations
- $f_{ij}$: flow of materials from facility $i$ to $j$
- $d_{kl}$: distance between locations $k$ and $l$
- $\pi$: one-to-one assignment with minimum cost

# QAP Formulation of Placement Problem

## Goal: find a placement with

$$\sum_k \mathcal{C}(k) \to \text{min}$$

## Flow

$$f_{ij} := \begin{cases} (d(i,j))^{-2} & \text{if spot } j \text{ is ``near'' spot } i, \\ 0 & \text{otherwise} \end{cases}$$

## Distance

$$d_{kl} := \sum_{t=1}^{T} d_{klt},$$

$$d_{klt} := \begin{cases} c \cdot \exp(\theta \cdot \lambda(p_k, t)) & \text{if } p_k \text{ is masked and } p_l \text{ unmasked in step } t, \\ 0 & \text{otherwise} \end{cases}$$

# QAP Heuristics

- The placement problem can be modeled as a QAP
- But QAP is known to be NP-hard
  - Generally impossible to solve (to optimalliy) for $n \geq 20$
- Several heuristics exist

### GRASP (Li, Pardalos and Resende, 1994)

- Greedy Randomized Adaptive Search Procedure
- Comprised of two phases
  1) Construction: buids a random feasible solution
  2) Local search: search a local optimum in the neighborhood
- GRASP with Path-Relinking (Oliveira *et al.*, 2004)

# Results on Small Artificial Chips

## Border Length minimization

| | Random | Row-epitaxial | | | GRASP with Path-Relinking | | |
|---|---|---|---|---|---|---|---|
| Dim | Cost | Cost | Red. | Time | Cost | Red. | Time |
| 6×6 | 1 989.20 | 1 714.60 | 13.80 | 0.01 | 1 672.20 | 15.94 | 2.73 |
| 7×7 | 2 783.20 | 2 354.60 | 15.40 | 0.02 | 2 332.60 | 16.19 | 6.43 |
| 8×8 | 3 721.20 | 3 123.80 | 16.05 | 0.03 | 3 099.13 | 16.72 | 12.49 |
| 9×9 | 4 762.00 | 3 974.80 | 16.53 | 0.05 | 3 967.20 | 16.69 | 25.96 |
| 10×10 | 5 985.20 | 4 895.60 | 18.20 | 0.06 | 4 911.40 | 17.94 | 47.57 |
| 11×11 | 7 288.40 | 5 954.40 | 18.30 | 0.10 | 5 990.73 | 17.80 | 87.48 |
| 12×12 | 8 714.00 | 7 086.20 | 18.68 | 0.11 | 7 159.80 | 17.84 | 152.42 |

Dim: chip dimension
Cost: total border length
Red.: reduction in %
Time: running time in seconds

# Results on Small Artificial Chips

## Conflict Index minimization

| | Random | Row-epitaxial | | | GRASP with Path-Relinking | | |
|---|---|---|---|---|---|---|---|
| Dim | Cost | Cost | Red. | Time | Cost | Red. | Time |
| 6×6 | 524.28 | 495.15 | 5.56 | 0.05 | 467.08 | 10.91 | 3.68 |
| 7×7 | 558.25 | 521.90 | 6.51 | 0.07 | 489.32 | 12.35 | 8.84 |
| 8×8 | 590.51 | 551.84 | 6.55 | 0.09 | 515.69 | 12.67 | 19.48 |
| 9×9 | 613.25 | 568.62 | 7.28 | 0.11 | 533.79 | 12.96 | 38.83 |
| 10×10 | 628.50 | 576.49 | 8.28 | 0.11 | 539.69 | 14.13 | 73.09 |
| 11×11 | 642.72 | 588.91 | 8.37 | 0.12 | 551.41 | 14.21 | 145.67 |
| 12×12 | 656.86 | 598.21 | 8.93 | 0.12 | 561.21 | 14.56 | 249.19 |

Dim: chip dimension
Cost: average conflict index
Red.: reduction in %
Time: running time in seconds

## Summary

- Conflict Index
    - New model for evaluating microarray layouts
- New approach to placement
    - Based on the Quadratic Assignment Problem
    - Good for very small regions... but too slow!

- Challenges
    - Make it faster?
    - Use it as a post-placement optimization
    - Formulation considering all embeddings

# Auf Wiedersehen!

**More info on**

http://gi.cebitec.uni-bielefeld.de/assb/chiplayout

**QAPLIB**

http://www.seas.upenn.edu/qaplib

- Thanks to Peter Hahn (University of Pennsylvania, USA)
- And thank you for your attention!