Microarray Layout and the Quadratic Assignment Problem

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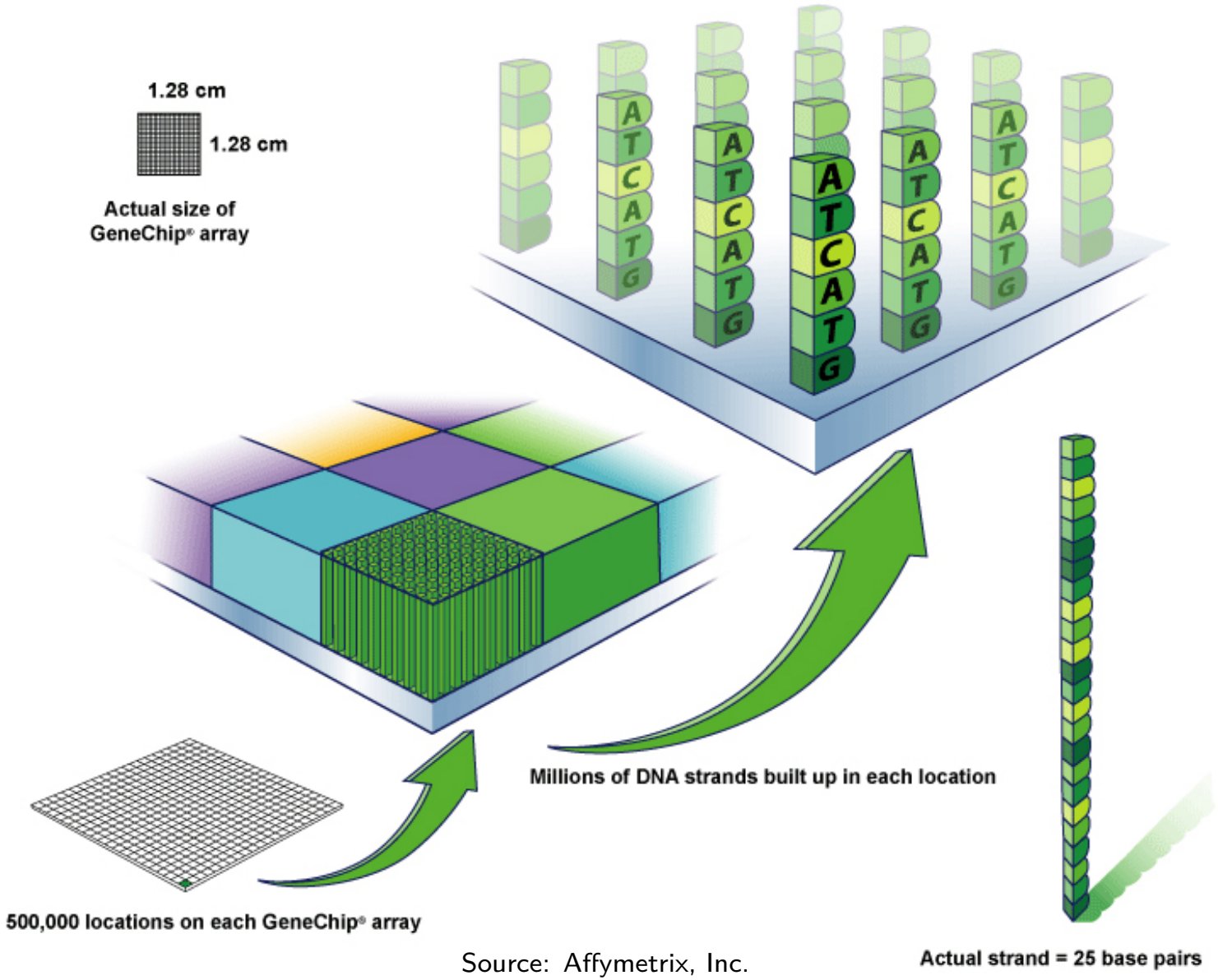
[3]Graduiertenkolleg Bioinformatik

German Conference on Bioinformatics, 2006

Outline

Outline

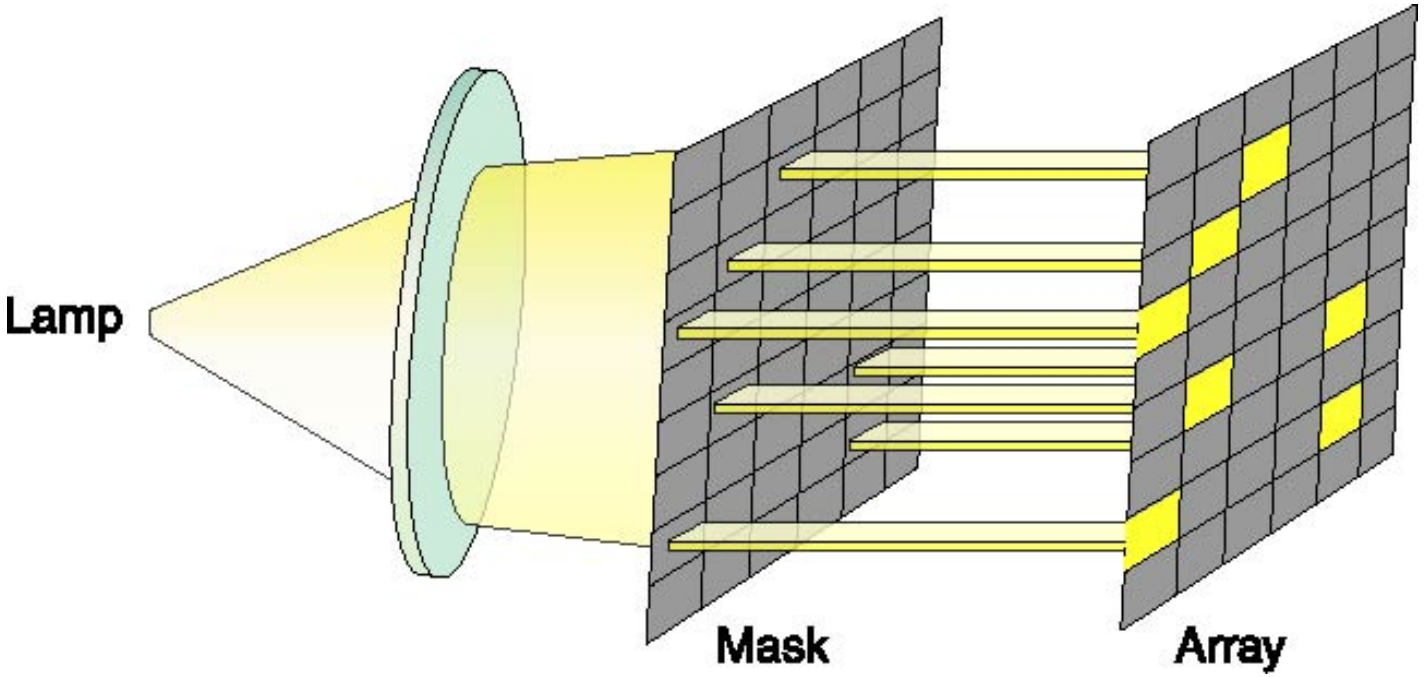
High-Density Oligonucleotide Microarrays



Source: Affymetrix, Inc.

Probe Synthesis with Photolitographic Masks

Source: Affymetrix, Inc.



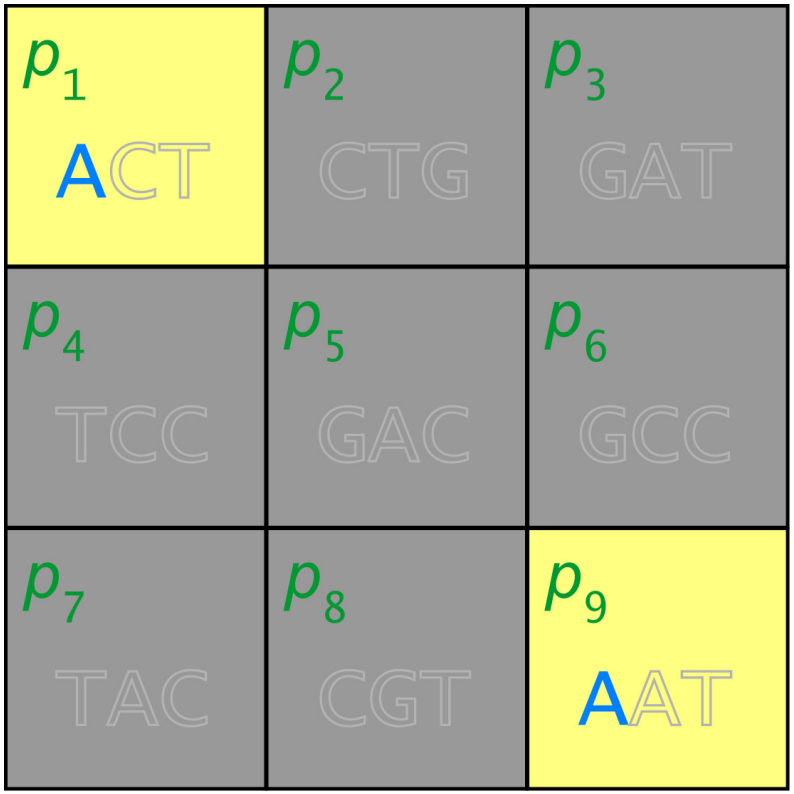
- Probes are synthesized on the chip in a series of steps
- Each step appends a particular nucleotide to selected regions
- Selection occurs by exposure to light directed by a mask

Deposition Sequence and Probe Embeddings

p_1 ACT	p_2 CTG	p_3 GAT
p_4 TCC	p_5 GAC	p_6 GCC
p_7 TAC	p_8 CGT	p_9 AAT

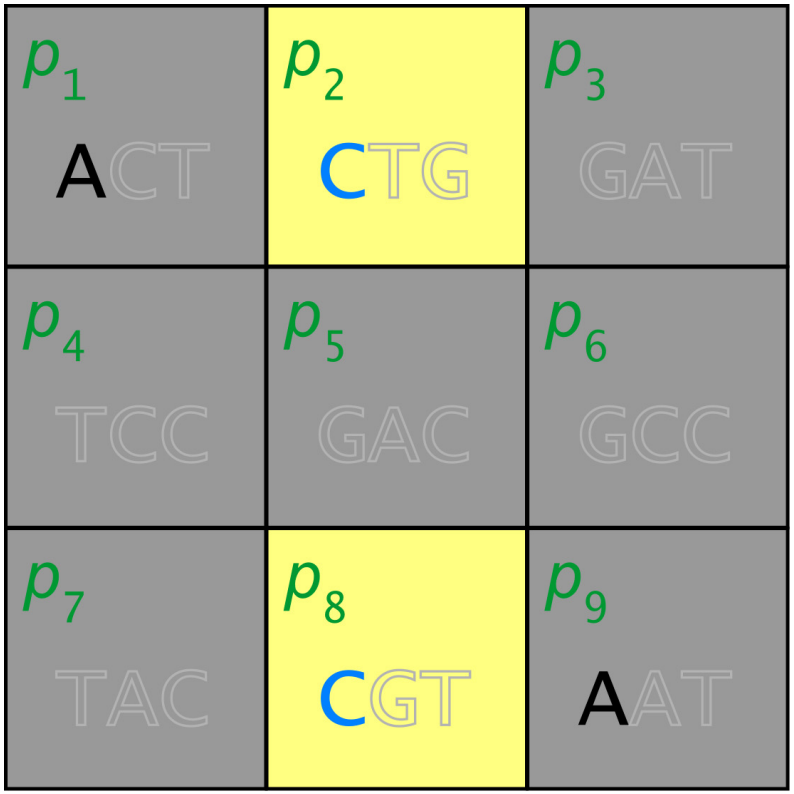
$$
\begin{aligned}
S &= \text{ACGTACGTACGT} \\
\varepsilon_1 &= \text{------------} \\
\varepsilon_2 &= \text{------------} \\
\varepsilon_3 &= \text{------------} \\
\varepsilon_4 &= \text{------------} \\
\varepsilon_5 &= \text{------------} \\
\varepsilon_6 &= \text{------------} \\
\varepsilon_7 &= \text{------------} \\
\varepsilon_8 &= \text{------------} \\
\varepsilon_9 &= \text{------------}
\end{aligned}
$$

Deposition Sequence and Probe Embeddings



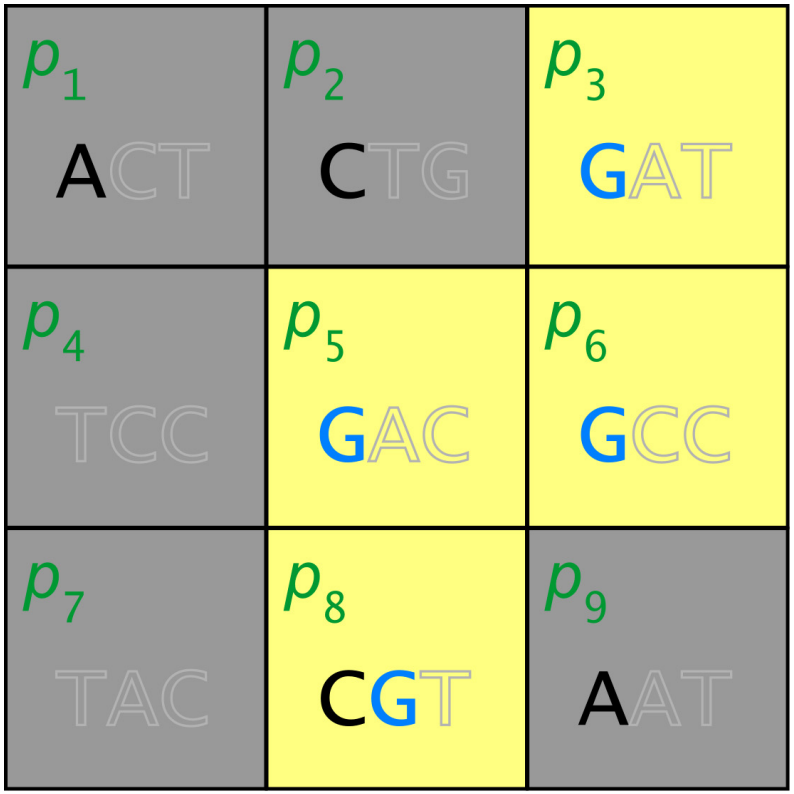
$$
\begin{aligned}
S &= \mathrm{ACGTACGTACGT} \\
\varepsilon_1 &= \mathrm{A}\text{-----------} \\
\varepsilon_2 &= \text{-----------} \\
\varepsilon_3 &= \text{-----------} \\
\varepsilon_4 &= \text{-----------} \\
\varepsilon_5 &= \text{-----------} \\
\varepsilon_6 &= \text{-----------} \\
\varepsilon_7 &= \text{-----------} \\
\varepsilon_8 &= \text{-----------} \\
\varepsilon_9 &= \mathrm{A}\text{-----------}
\end{aligned}
$$

Deposition Sequence and Probe Embeddings



$$
\begin{aligned}
S &= \text{ACGTACGTACGT} \\
\varepsilon_1 &= \text{A----------} \\
\varepsilon_2 &= \text{-C----------} \\
\varepsilon_3 &= \text{----------} \\
\varepsilon_4 &= \text{----------} \\
\varepsilon_5 &= \text{----------} \\
\varepsilon_6 &= \text{----------} \\
\varepsilon_7 &= \text{----------} \\
\varepsilon_8 &= \text{-C----------} \\
\varepsilon_9 &= \text{A----------}
\end{aligned}
$$

Deposition Sequence and Probe Embeddings



$$
\begin{aligned}
S &= \text{ACGTACGTACGT} \\
\varepsilon_1 &= \text{A----------} \\
\varepsilon_2 &= \text{-C---------} \\
\varepsilon_3 &= \text{--G---------} \\
\varepsilon_4 &= \text{----------} \\
\varepsilon_5 &= \text{--G---------} \\
\varepsilon_6 &= \text{--G---------} \\
\varepsilon_7 &= \text{----------} \\
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\end{aligned}
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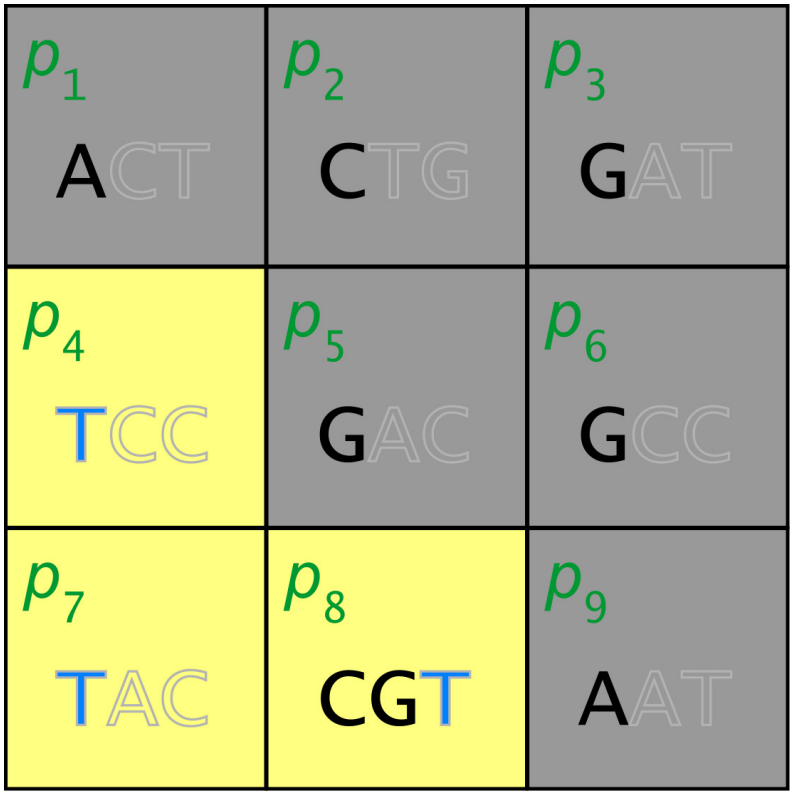
Deposition Sequence and Probe Embeddings



$$
\begin{aligned}
S &= \text{ACGTACGTACGT} \\
\varepsilon_1 &= \text{A----------} \\
\varepsilon_2 &= \text{-C---------} \\
\varepsilon_3 &= \text{--G--------} \\
\varepsilon_4 &= \text{---T-------} \\
\varepsilon_5 &= \text{--G--------} \\
\varepsilon_6 &= \text{--G--------} \\
\varepsilon_7 &= \text{---T-------} \\
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$$
\begin{aligned}
S &= \text{ACGTACGTACGT} \\
\varepsilon_1 &= \text{A----C-T----} \\
\varepsilon_2 &= \text{-C------T--G-} \\
\varepsilon_3 &= \text{--G-A--T----} \\
\varepsilon_4 &= \text{---T-C---C--} \\
\varepsilon_5 &= \text{--G-A----C--} \\
\varepsilon_6 &= \text{--G--C---C--} \\
\varepsilon_7 &= \text{---TAC------} \\
\varepsilon_8 &= \text{-CGT--------} \\
\varepsilon_9 &= \text{A---A------T}
\end{aligned}
$$

Deposition Sequence and Probe Embeddings

p_1 ACT	p_2 CTG	p_3 GAT
p_4 TCC	p_5 GAC	p_6 GCC
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S = ACGTACGTACGT

ε_1 = A----C-T----

ε_2 = -C------T--G-

ε_3 = --G-A--T----

ε_4 = ---T-C---C--

ε_5 = --G-A----C--

ε_6 = --G--C---C--

ε_7 = ---TAC------

ε_8 = -CGT--------

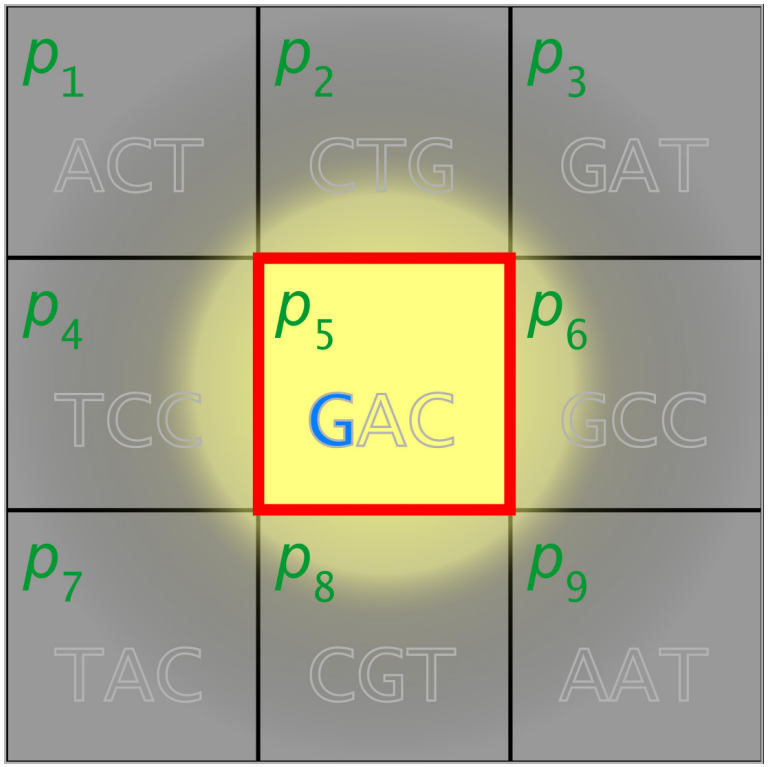
ε_9 = A---A------T

ε'_9 = A--------A--T

Right-most: ε''_9 = ----A---A--T

Left-most: ε'''_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

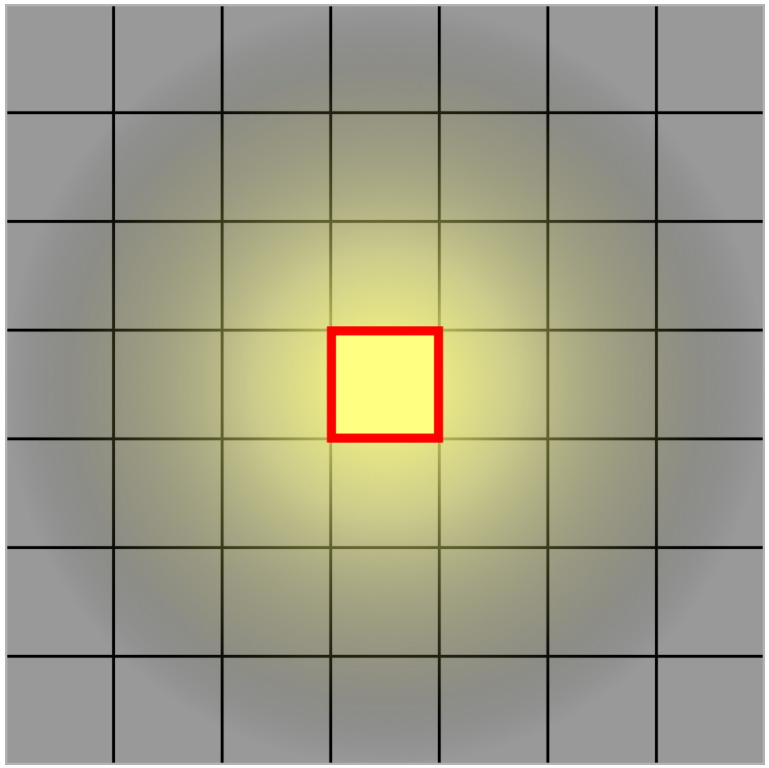
Border Length Minimization Problem (Hannenhalli et al., 2002)

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

Outline

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

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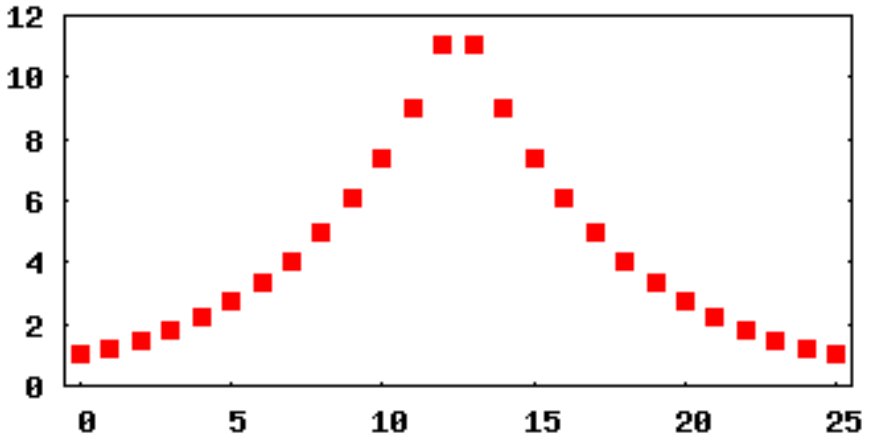


Position-dependent weights

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

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, ℓ_p is the length of probe p, $c > 0$ and $\theta > 0$ are constants.

Border Length and Conflict Index

Redefine δ and ω 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 $\sum_p \mathcal{C}(p) = \sum_{t=1}^{T} \mathcal{B}_t$
- Total border length can be modeled as total conflict index for a particular choice of δ and ω
- 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

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

Outline

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)

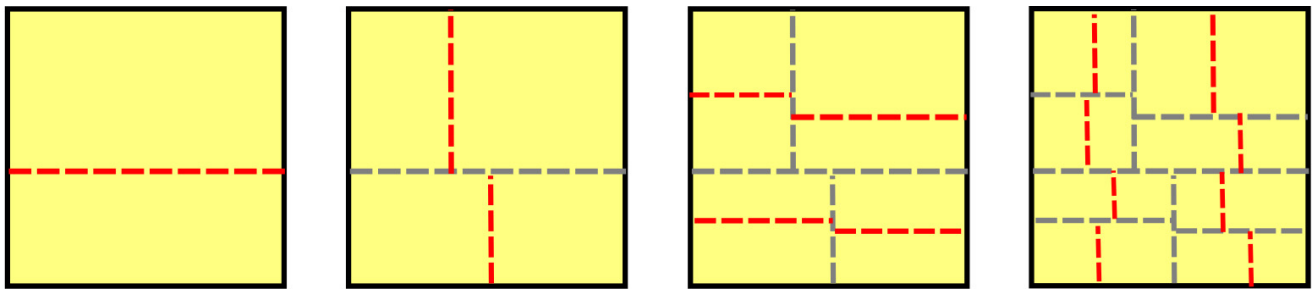
- Based on the Optimum Single Probe Embedding (OSPE)
  - Re-embed a probe optimally in regards to its neighbors
  - Dynamic programming, like a sequence alignment

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 (QAP)

Definition

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

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

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
- π: one-to-one assignment with minimum cost

QAP Formulation of Placement Problem

QAP

- Given $n \times n$ real-valued matrices F and D
- Find a permutation π of $\{1, 2, \ldots n\}$ such that

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

Placement as a QAP

- Given a set of probes with fixed embeddings
- Find placement on the chip such that

$$\sum_{k} \mathcal{C}(k) \rightarrow \min$$

QAP Formulation of Placement Problem

Goal: find a placement with

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

"Flow" f_{ij}: distance between spots i and j

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

"Distance" d_{kl}: conflicts between probes k and l

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

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

QAP Heuristics

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

GRASP (Li, Pardalos and Resende, 1994)

- Greedy Randomized Adaptive Search Procedure
- Comprised of two phases
  1) Construction: builds 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

Applications

- QAP is good for small regions...
  - But not feasible for an entire microarray chip

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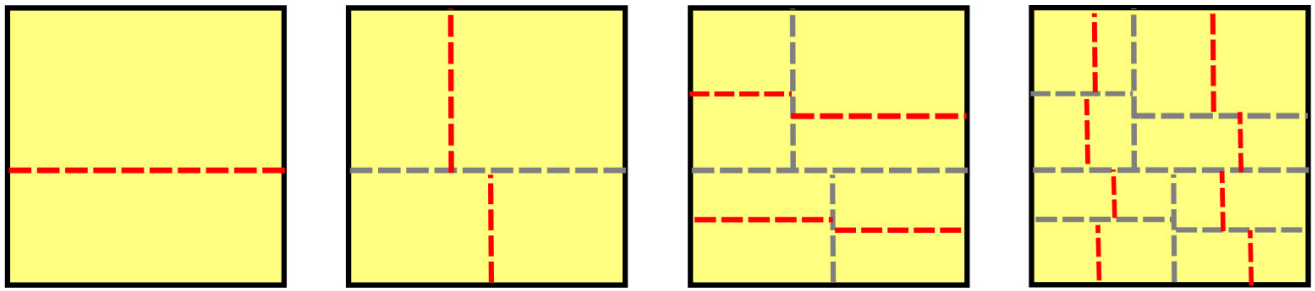
- QAP is good for small regions...
  - But not feasible for an entire microarray chip
- Two applications:
  1) Combine it with a partitioning algorithm



Applications

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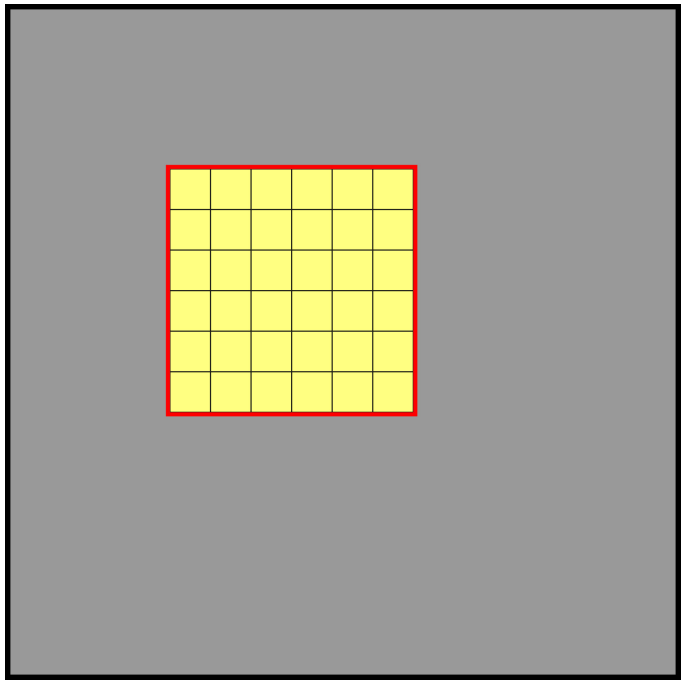
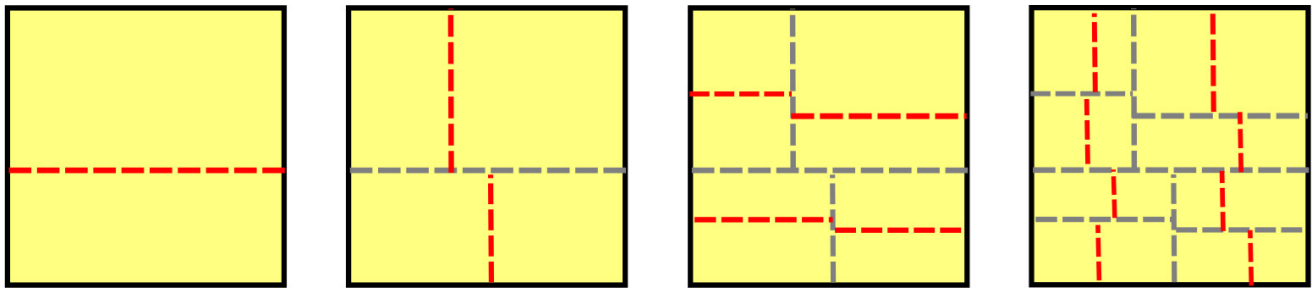
- Two applications:
  1) Combine it with a partitioning algorithm
  2) Use it as a post-placement optimization inside a sliding-window





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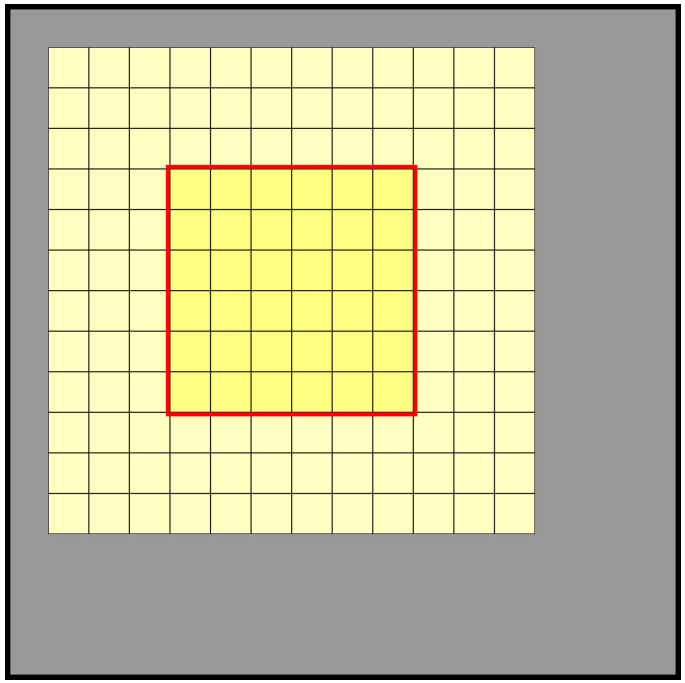

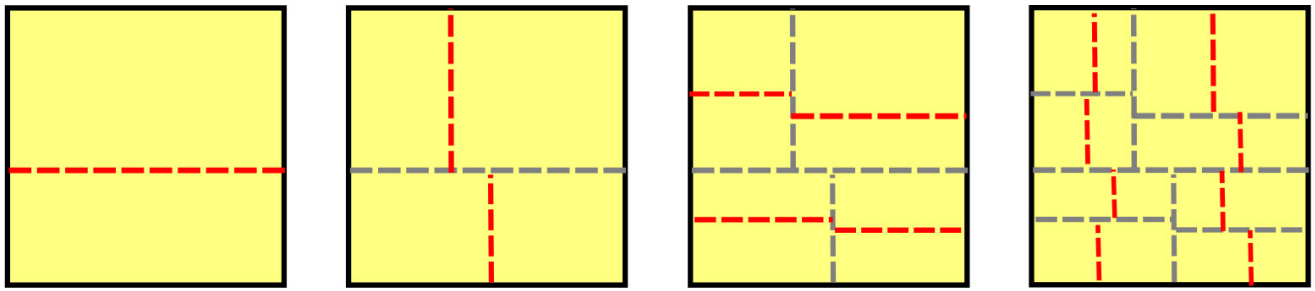

Summary

- Conflict Index
  - New model for evaluating microarray layouts
- New approach to placement
  - Based on the Quadratic Assignment Problem

- Challenges
  - Faster or better QAP heuristics?
  - Adapt QAP for 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!